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Susceptibility to Infection-Induced Acute Encephalopathy 3 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Acute Necrotizing Encephalopathy (ANE1)

Derek Neilson, MD[1]

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Infection-induced acute encephalopathy 3 (IIAE3) is the susceptibility to recurrent acute necrotizing encephalopathy (ANE) caused by a heterozygous pathogenic variant in *RANBP2.* ANE refers to the specific neurologic presentation in which bilateral symmetric thalamic, midbrain, and/or hindbrain lesions occur within days following the onset of an acute viral illness caused by influenza A, influenza B, parainfluenza II, human herpes virus 6, coxsackie virus, or an enterovirus. Although most IIAE3 occurs before age six years, first episodes have been observed in teenagers and adults. ANE begins within 12 hours to three or four days of the first awareness of viral symptoms (fever, cough, rhinorrhea, vomiting, diarrhea, and malaise). The most common sign of ANE is lethargy that progresses to coma (which may last for weeks) and seizures (in 50%). One third of affected individuals die during the acute phase of the encephalopathy; of the survivors, one half have permanent neurologic damage and the remainder have no discernible residual symptoms. Fifty per cent of persons with IIAE3 will have at least one repeat episode and some will have multiple repeat episodes

Diagnosis/testing

IIAE3 is suspected in individuals with typical clinical and MRI findings, and is confirmed in those with a heterozygous pathogenic variant in *RANBP2.*

Management

Treatment of manifestations: Treatments for IIAE3 remain anecdotal and it should be noted that patients have recovered without specific intervention. Treatment is aimed at reducing the inflammatory state by

Author Affiliation: 1 Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Email: derek.neilson@cchmc.org.

administration of corticosteroids during an acute episode of encephalopathy (not supported by data from IIAE-3-specific studies) as well as IVIg, plasmapheresis, and TNFα antagonists with varied, but overall limited, therapeutic effects.

Prevention of primary manifestations: Routine vaccinations and yearly influenza vaccinations are recommended, although there are theoretic concerns for live influenza and cellular pertussis preparations. No studies have suggested that vaccinations cause acute necrotizing encephalopathy (ANE) in an individual heterozygous for an *RANBP2* pathogenic variant.

Surveillance: No standard tests allow prediction of the triggering of an ANE event or progression of an event once one occurs.

Agents/circumstances to avoid: Avoid individuals who are ill with an infectious disease and adhere to strict precautions regarding hand washing. Based on a single case report of ANE in one individual (not known to have a *RANBP2* pathogenic variant), avoidance of cellular pertussis in DTaP immunization is recommended.

Evaluation of relatives at risk: In a family with IIAE3, molecular genetic testing of at-risk first-degree relatives, especially children, is warranted so that those who have inherited the *RANBP2* pathogenic variant can benefit from prompt intervention in the early stages of ANE.

Genetic counseling

Susceptibility to IIAE3 is inherited in an autosomal dominant manner. To date the majority of individuals diagnosed with IIAE3 have a parent who is heterozygous for a *RANBP2* pathogenic variant; however, due to reduced penetrance, the parent may not have manifested the disease state. Also, a proband with susceptibility to IIAE3 may have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with susceptibility to IIAE3 has a 50% chance of inheriting the pathogenic variant. When the *RANBP2* pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk is possible.

Diagnosis

Infection-induced acute encephalopathy 3 (IIAE3) refers to the susceptibility to recurrent acute necrotizing encephalopathy (ANE) caused by mutation of *RANBP2* that is inherited in an autosomal dominant manner. Acute necrotizing encephalopathy refers to the specific neurologic presentation in which bilateral symmetric thalamic, midbrain, and/or hindbrain lesions occur within days following the onset of an acute viral illness [Mizuguchi et al 1995].

Suggestive Findings

Infection-induced acute encephalopathy 3 (IIAE3) **is suspected** in individuals with the following:

- No preceding developmental or neurologic defects [Mizuguchi et al 1995, Neilson et al 2003]
- Signs at onset that can be attributed to a viral trigger, such as fever, cough, rhinorrhea, vomiting, diarrhea, and malaise
  - Viruses known to precipitate ANE include influenza A, influenza B, parainfluenza II, human herpesvirus 6, coxsackie virus, and enteroviruses [Neilson 2010].
  - The only bacterium known to precipitate ANE is *Mycoplasma pneumonia* [Ashtekar et al 2003].
- Onset of ANE beginning within 12 hours to three or four days of the first awareness of viral symptoms. The most common sign of ANE is lethargy that progresses to coma and seizures (50%).

- At the time of hospital admission, brain MRI demonstrating:
  - T_2- and FLAIR-weighted hyperintensities in the bilateral thalami, midbrain, cerebellum, pons, and brain stem [Mizuguchi et al 1995, Neilson et al 2003];
  - Additional involved regions including the limbic system (e.g., the amygdala, mammillary bodies) and lateral regions such as the claustra and external capsules [Neilson 2010];

    Note: The presence of lesions in these areas should prompt consideration of IIAE3, even in the absence of recurrence or family history [Neilson 2010].
  - Less commonly, involvement of the basal ganglia [Neilson 2010].

    Note: It has been reported that gadolinium can identify lesions prior to their recognition on noncontrast MRI [Yoshida et al 2013].
- Pathologic findings that are similar to those of Leigh syndrome and Wernicke encephalopathy (i.e., regions of neuronal necrosis, capillary proliferation and dilation, hemorrhage, and edema, without local infiltration of other inflammatory cells) [Neilson 2010]. The axis for these lesions would suggest a vascular distribution coming from the posterior circulation [Neilson 2010]. The distribution of lesions matches the MRI findings.

Establishing the Diagnosis

The diagnosis of IIAE3 is based on the presence of a heterozygous pathogenic variant in *RANBP2* identified by molecular genetic testing (Table 1). Only three single-nucleotide variants – clustered in the "leucine-rich" domain (exons 12 and 14) – have been identified to date (see Molecular Genetics) [Neilson et al 2009].

Table 1. Molecular Genetic Testing Used in Susceptibility to Infection-Induced Acute Encephalopathy 3

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method
RANBP2	Sequence analysis [2]	27/86 (31%) [3]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
3. Author [unpublished data]. Denominator represents unrelated probands who either have a positive family history or represent simplex cases (i.e., a single occurrence in a family). Each proband independently fulfilled criteria for ANE.

Clinical Characteristics

Clinical Description

Most infection-induced acute encephalopathy 3 (IIAE3) (which by definition is caused by mutation of *RANBP2*) occurs before age six years, with the majority of cases occurring between age nine months and two years [Neilson et al 2003]. Although the number of first episodes decreases with age, first episodes of IIAE3 have been observed in teenagers and adults [Neilson 2010].

Acute necrotizing encephalopathy (ANE) is always preceded by a febrile infection that is usually viral [Mizuguchi et al 1995]. Viruses known to precipitate ANE include influenza A, influenza B, parainfluenza II, human herpesvirus 6, coxsackie virus, and enteroviruses [Neilson 2010]. *Mycoplasma pneumoniae* has also been implicated [Ashtekar et al 2003]. Initial symptoms are attributable to the virus and may include fever, vomiting, diarrhea, cough, rhinorrhea, or rash.

The progression to acute neurologic dysfunction may occur within hours to days following the onset of the febrile infection. Initial manifestations include decreased consciousness and seizures. Neurologic findings that may accompany the encephalopathy include hallucination, ataxia, hypotonia, hypertonia, and decerebrate or decorticate posturing.

Most affected persons present with or progress to coma [Mizuguchi et al 1995, Neilson 2010]. The comatose state, which may last from days to months, is usually on the order of weeks.

One third of affected individuals die during the acute phase of the encephalopathy [Mizuguchi 1997, Neilson et al 2003]. Initially, all survivors of ANE will demonstrate losses of multiple developmental skills such as walking, speaking, and self-care. These may be regained over a period of weeks to months [Neilson et al 2003]. Of the survivors, one half are left with permanent neurologic damage and the remainder have no discernible residual symptoms or intellectual disability [Mizuguchi 1997, Neilson et al 2003].

Fifty per cent of persons with IIAE3 will have at least one repeat episode and some will have multiple repeat episodes [Neilson 2010]. Whereas additional episodes are most likely to take place in childhood, recurrence in teenagers and adults has been reported. Repeat episodes presumably result in additional cellular damage and, thus, outcomes are progressively worse, regardless of the degree of initial clinical recovery [Neilson et al 2003].

Laboratory findings. In the acute phase in persons with sporadic ANE, IL6 and TNFα have been inconsistently elevated in the serum and CSF [Kansagra & Gallentine 2011] (see Differential Diagnosis). These analytes have not been systematically evaluated in IIAE3.

Genotype-Phenotype Correlations

The three single nucleotide variants identified in *RANBP2* (see Molecular Genetics) result in the same phenotype [Neilson et al 2009].

Penetrance

Penetrance is incomplete and age dependent. Forty percent of heterozygotes for a *RANBP2* pathogenic variant will manifest an episode of acute necrotizing encephalopathy (ANE); 50% of such episodes occur before age two years. A first episode becomes less likely with age, but can occur in adulthood [Neilson et al 2009].

Anticipation

Genetic anticipation does not occur with IIAE3, although families may appear to have anticipation on the basis of earlier recognition of the diagnosis in subsequent generations [Neilson et al 2009].

Nomenclature

The term "acute necrotizing encephalopathy" (ANE) continues to be used for ANE that is sporadic (i.e., a single occurrence in a family of unknown cause).

Infection-induced acute encephalopathy 3 (IIAE3) is reserved for ANE with a documented *RANBP2* pathogenic variant.

The infection-induced acute encephalopathy (IIAE) series describes genetic predispositions to CNS dysfunction following infections:

- IIAE1, IIAE2, IIAE5, and IIAE6 refer to genetic variants that allow herpes simplex virus to invade the CNS.
- IIAE3 refers to non-neuronopathic infections of different types that can trigger encephalopathy without evidence of direct CNS invasion.

- IIAE4 refers specifically to influenza-mediated encephalopathy, also without CNS invasion factor [Shinohara et al 2011].

ANE1 defines the previous symbol assigned to the 2q12.1-2q13 genomic locus in which *RANBP2* pathogenic variants were eventually identified. (The ANE numbering system [i.e., ANE2, ANE3, and so on] was started in recognition that other kindreds with ANE do not show linkage to the same region [Neilson 2010] ; however, to date, no families have been large enough to allow genetic studies to associate chromosome loci or genes with these additional loci.)

Note: While ANE caused by mutation of *RANBP2* has been termed ANE1 in some publications, it has been termed IIAE3 in OMIM.

Prevalence

Acute necrotizing encephalopathy (ANE) is underreported; the prevalence and incidence of ANE remain unknown. Due to ascertainment bias, it is not possible to estimate the proportion of ANE that results from mutation of *RANBP2* (and thus is classified as infection-induced acute encephalopathy 3 [IIAE3]).

- In a two-year surveillance study of influenza in the UK, four cases of ANE were identified, suggesting an incidence in the total population of approximately one per 30 million person-years [Goenka et al 2014]. However, this would be an underestimate as influenza is not the only cause of ANE.
- An estimate of ten to 50 cases of ANE in the United States per year seems appropriate [Author, personal prediction based on observed cases] and may depend on the viral strains present in a given year.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline mutation of *RANBP2*.

Sporadic cancers (including myelomonocytic leukemia and inflammatory myofibroblastic tumor) occurring as single tumors in the absence of any other findings of this syndrome may harbor somatic pathogenic variants in *RANBP2* that are **not** present in the germline; thus, predisposition to these tumors is not heritable. For more details see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Other causes of acute necrotizing encephalopathy (ANE). ANE occurs in both familial and sporadic forms. In a child with a first onset, certain brain MRI findings, such as the presence of lesions in the limbic system or external capsule, may provide clues to identify IIAE3, but otherwise the familial and sporadic forms are indistinguishable [Neilson 2010]. While multiple different viruses can trigger ANE, no other genetic predispositions for ANE have been identified.

Evidence for locus heterogeneity. Locus heterogeneity is suggested by families in which multiple members have ANE, but do not have pathogenic variants in *RANBP2* and whose phenotype fails to show linkage to the *RANBP2* region [Neilson et al 2009, Marco et al 2010]. For these additional families, the rarity of the condition favors a genetic predisposition rather than chance co-occurrence.

IIAE4, influenza-associated encephalopathy (OMIM 614212). The initial presentation is very similar to IIAE3, with acute neurologic decompensation following an influenza infection; however, brain MRI demonstrates either no abnormalities or diffuse swelling. Thermolabile alleles of carnitine palmitoyl transferase II (CPT) that are prevalent in Japan and inactivate CPTII during periods of fever have been implicated as a susceptibility factor [Shinohara et al 2011].

Other disorders that can present with findings similar to those of IIAE3

- **Acute bilateral striatal necrosis** can be precipitated commonly by *Mycoplasma pneumoniae* [Larsen & Crisp 1996]. It presents as a febrile encephalopathy with symmetric lesions detected on brain MRI primarily in the putamen and globus pallidum. No contributing gene has been identified.
- **Alpers-Huttenlocher syndrome (AHS)** (see *POLG*-Related Disorders). One of the most severe phenotypic manifestations in the spectrum of *POLG*-related disorders, AHS is characterized by a progressive and ultimately severe encephalopathy with intractable epilepsy and hepatic failure. The age of onset, the rate of neurologic degeneration, the presence of hepatic failure, and the age of death vary. The brain MRI lesions of AHS are similar to those of ANE. Typically a childhood-onset disorder, AHS does not require a preceding inflammatory event. Inheritance is autosomal recessive. Biallelic pathogenic variants in *POLG* are causative.
- **Leigh syndrome (LS) and other mitochondrial disorders** (see Mitochondrial Disorders Overview). LS manifests as a progressive neurodegenerative disorder resulting from a variety of defects in mitochondrial function. Blood lactate is typically elevated, but can be variable. LS can become acutely worse during febrile infections, possibly producing a presentation similar to ANE. While the basal ganglia are most characteristically affected, other brain regions such as the thalami can be symmetrically affected as well [Baertling et al 2014]. The histopathologic characteristics of ANE overlap with those of LS [Mizuguchi et al 1995].
- **Acute disseminated encephalomyelitis (ADEM)** is a demyelinating disorder that is considered to be autoimmune in nature. It affects the CNS white matter, but can involve gray matter as well, presenting with an encephalopathy. The triggers for this disorder, which include vaccinations and infections, precede the encephalopathy by weeks rather than days. Although predominance of white matter lesions and asymmetric involvement support the diagnosis of ADEM rather than ANE, involvement of the thalami can make it difficult to distinguish the two [Alper 2012].
- **Multiple sclerosis (MS)** is not a true consideration in the differential diagnosis; however, in the past – for lack of a better diagnosis – some adults with ANE were diagnosed with "atypical MS." When MS or similar terminology is used to describe a finding in a family member, further investigation and review of medical records are warranted to ensure its accuracy. An experienced neurologist will be able to differentiate the brain MRI lesions of ANE from the lesions found in MS, which tend to be multifocal white matter lesions [Karussis 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with susceptibility to infection-induced acute encephalopathy 3 (IIAE3), the following evaluations are recommended after an episode of acute necrotizing encephalopathy (ANE):

- Brain MRI during a quiescent period. This should demonstrate resolution of the edema signals and may reveal regions of necrosis. This interval baseline will be helpful in distinguishing new versus old lesions in subsequent febrile events.
- Rehabilitation/OT/PT consultation
- Neurology consultation
- Clinical genetics consultation

Treatment of Manifestations

Treatment has been aimed at reducing the inflammatory state [Okumura et al 2009, Bergamino et al 2012].

During an acute episode of encephalopathy, early administration of corticosteroids has been associated with improved outcomes in patients with sporadic ANE [Okumura et al 2009]. Although this treatment course is also advocated for IIAE3, no specific studies have been performed to support that.

Anecdotally, treatment has mirrored that of acute demyelinating encephalomyelopathy (ADEM) with the use of steroids, IVIg, and plasmapheresis. TNFα antagonists have also been used. Because the diagnosis of ANE is usually made days into the encephalopathy, initiation of therapy occurs after the onset of damage. Thus, anecdotally, these interventions have shown varied, but overall limited, therapeutic effects.

Repeat episodes of encephalopathy presumably result in cellular damage and, thus, outcomes become progressively worse [Neilson et al 2003], prompting the need for close attention to new febrile events and early intervention as follows:

- Prior identification of an *RANBP2* pathogenic variant in an affected individual allows early recognition of an ANE episode and prompt steroid therapy, which may result in a reduction in disease severity.
- With behavioral changes during febrile episodes, early evaluation by a neurologist with prompt hospitalization, CNS imaging, and initiation of steroid therapy may provide the best chance to terminate an ANE episode before damage occurs.

Prevention of Primary Manifestations

Routine vaccinations and yearly influenza vaccinations are recommended, but caution with certain live virus vaccines may need to be observed (see Agents/Circumstances to Avoid). No evidence exists to suggest that vaccinations cause acute necrotizing encephalopathy (ANE) in an individual heterozygous for an *RANBP2* pathogenic variant.

Surveillance

No standard tests allow prediction of the triggering of an ANE event or progression of an event once one occurs.

In intervals between ANE events neurologic function is stable. Follow-up evaluations focus on developmental progression and addressing functional deficits related to neurologic damage. In the absence of other risks for seizures, anticonvulsant therapy started during an ANE event can often be discontinued.

Agents/Circumstances to Avoid

Avoid individuals who are ill with an infectious disease and adhere to strict precautions regarding hand washing.

Only one episode of ANE following an immunization has been reported: cellular pertussis was given to a child age six months representing a simplex case (i.e., a single occurrence in a family) in whom *RANBP2* molecular genetic testing was not performed [Aydin et al 2010]. Because the likely causative component was the cellular pertussis, the acellular DTaP is preferred.

In mice, intranasal inoculation of certain influenza subtypes can result in CNS invasion [Shinya et al 2000]. Although this is unlikely with the live attenuated influenza virus, it may be preferable to choose an injectable form instead.

Evaluation of Relatives at Risk

In a family with IIAE3 in which the disease-associated *RANBP2* pathogenic variant has been identified, molecular genetic testing of at-risk first-degree relatives, especially children, is warranted so that those who have inherited the *RANBP2* pathogenic variant can benefit from prompt intervention in the early stages of ANE (see Treatment of Manifestations).

The ability to clarify the genetic status of at-risk relatives also reduces unnecessary utilization of resources, such as emergency room visits, for those who have not inherited the *RANBP2* pathogenic variant.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Susceptibility to infection-induced acute encephalopathy 3 (IIAE3) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with susceptibility to IIAE3 have a parent who is heterozygous for a *RANBP2* pathogenic variant; however, due to incomplete penetrance, the parent may not have manifested the disease state.
- A proband with susceptibility to IIAE3 may have the disorder as the result of a *de novo* pathogenic variant. Although the proportion of cases caused by *de novo* pathogenic variants is unknown, to date the majority of molecularly confirmed cases have resulted from inherited pathogenic variants.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include testing for the pathogenic variant identified in the proband. Evaluation of parents may determine that one parent has the pathogenic variant but has escaped previous ascertainment because of a milder phenotype, an alternate diagnosis, reduced penetrance, or late occurrence of a first episode. Therefore, an apparently negative family history cannot be confirmed until molecular genetic testing has been performed.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent has the *RANBP2* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The sibs of a proband with clinically unaffected parents are still at increased risk for susceptibility to IIAE3 because of the possibility of reduced penetrance in a parent.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with susceptibility to infection-induced acute encephalopathy 3 has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for the *RANBP2* pathogenic variant identified in the proband, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives so that those who have inherited the *RANBP2* pathogenic variant can benefit from prompt intervention in the early stages of ANE.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant, the variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults at risk for IIAE3.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *RANBP2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for susceptibility to infection-induced acute encephalopathy 3 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While decisions regarding prenatal testing are the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824

Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
Encephalopathy Information Page

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Susceptibility to Infection-Induced Acute Encephalopathy 3: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
RANBP2	2q13	E3 SUMO-protein ligase RanBP2	RANBP2 database	RANBP2	RANBP2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Susceptibility to Infection-Induced Acute Encephalopathy 3 (View All in OMIM)

601181	RAN-BINDING PROTEIN 2; RANBP2
608033	ENCEPHALOPATHY, ACUTE, INFECTION-INDUCED, SUSCEPTIBILITY TO, 3; IIAE3

Gene structure. *RANBP2* encodes for a 29-exon gene with a full-length spliced transcript of 11711 bp. *RANBP2* is known to be the original gene in a series of gene duplication events leading to a series of hybrid genes designated as *RGPD1* through *RGPD8* [Ciccarelli et al 2005]. Duplications and deletions arising from nonhomologous recombination occur throughout this region, but to date have not been associated with ANE. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. In an event specific to primates, a series of rearrangement and duplication events has led to eight derivative genes termed "*RGPD*s" [Ciccarelli et al 2005] which encode for "RANBP2-like and GRIP domain containing proteins." Most of the benign variants in dbSNP reported in the exon coding sequence of *RANBP2* are not true polymorphisms, but are stable base substitutions that are nonspecifically amplified from the *RGPD*s. Special primer conditions must be used when Sanger sequencing the primary *RANBP2* gene [Neilson et al 2009]. Caution must be used when interpreting normal and abnormal alleles, as they may represent nonspecific amplifications of the derivative paralogs.

Pathogenic variants. See Table 2.

Table 2. *RANBP2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1754C>T	p.Thr585Met	NM_006267.4 NP_006258.3
c.1958C>T	p.Thr653Ile	
c.1966A>G	p.Ile656Val	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *RANBP2* encodes a mature protein of 3224 amino acids. Its molecular weight is approximately 358 kd, for which the protein was previously named NUP358. RANBP2 has multiple functional domains and multiple roles within the cell. It contains a nuclear envelope localizing signal, four RAN binding domains, a series of zinc finger repeats, an E3 SUMO ligase domain, and a cyclophilin A domain [Neilson 2010].

RANBP2 contributes to the nuclear filaments present on the cytoplasmic surface of the nuclear pore. RANBP2 has been shown to participate in multiple functions including nuclear import and export, intracellular trafficking, mitochondrial distribution, and maintenance of chromosomal mitotic segregation. It also serves as a nuclear docking site for certain viruses, such as HIV [Neilson 2010, Di Nunzio et al 2012].

Abnormal gene product. At present, it is unclear how the *RANBP2* protein causes the disease state.

Cancer and Benign Tumors

Sporadic cancers (including myelomonoctyic leukemia and inflammatory myofibroblastic tumor) occurring as single tumors in the absence of any other findings of this syndrome may harbor somatic variants in *RANBP2* that are not present in the germline; thus, predisposition to these tumors is not heritable. A recombination between *RANBP2* and *ALK* resulting in a chimeric fusion protein has been described most commonly [Patel et al 2007, Chen & Lee 2008, Li et al 2013, Lim et al 2014]. The amino terminal portion of RANBP2 causes ALK to be localized and inappropriately active at the nuclear surface.

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Chapter Notes

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