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Nijmegen Breakage Syndrome

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Summary

Clinical characteristics

Nijmegen breakage syndrome (NBS) is characterized by progressive microcephaly, early growth deficiency that improves with age, recurrent respiratory infections, an increased risk for malignancy (primarily lymphoma), and premature ovarian failure in females. Developmental milestones are attained at the usual time during the first year; however, borderline delays in development and hyperactivity may be observed in early childhood. Intellectual abilities tend to decline over time. Recurrent pneumonia and bronchitis may result in respiratory failure and early death. Other reported malignancies include solid tumors (e.g., medulloblastoma, glioma, rhabdomyosarcoma).

Diagnosis/testing

The diagnosis of NBS is established in a proband with characteristic clinical features and biallelic pathogenic variants in *NBN* on molecular genetic testing and/or absent nibrin protein on immunoblotting assay.

Management

Treatment of manifestations: Standard antimicrobial therapies for infections; immunoglobulin replacement therapy in individuals with severe hypogammaglobulinemia and frequent infections; acellular vaccines; standard treatment of bronchiectasis and pulmonary infections; chemotherapy protocols for lymphoid malignancies adapted to individual tolerance; treatment of solid tumors adapted to individual tolerance; consideration of hematopoietic stem cell transplantation; hormone replacement therapy for females who have hypergonadotropic hypogonadism.

Surveillance:

- **For affected individuals.** Periodic follow up to monitor physical growth, infection frequency, and developmental progress; lifelong monitoring of immune biomarkers; monitor for malignancy and

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particularly in those with weight loss, fever, weakness, enlargement of peripheral lymph nodes, dyspnea, cough, and hepatosplenomegaly (assessment should be considered using ultrasonography, MRI, biopsy); monitor pubertal progression in both sexes and for premature ovarian insufficiency in females; monthly breast self-examination when hormone replacement therapy is administered; assess cognitive developmental and intellectual abilities before starting school and follow up periodically.
- **For heterozygous adults.** Monitor for malignancy, particularly breast cancer in women and prostate cancer in men.

Agents/circumstances to avoid: Because the cells from individuals with NBS are radiosensitive in vitro, doses of radiation used in radiotherapy need to be reduced. Unnecessary exposure to imaging studies that use ionizing radiation (plain radiograph, CT scan) should be avoided and use of MRI and/or ultrasound considered. Live vaccines (e.g., live vaccines for tuberculosis, measles, mumps, rubella, and varicella) should not be given.

Evaluation of relatives at risk: It is appropriate to offer molecular genetic testing for the familial *NBN* pathogenic variants to apparently asymptomatic adult relatives of an affected individual in order to identify family members who are heterozygous for an *NBN* pathogenic variant and would benefit from monitoring for malignancy.

Genetic counseling

NBS is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of inheriting both pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being a heterozygote, and a 25% chance of inheriting neither of the familial *NBN* pathogenic variants. Heterozygotes are not at risk for NBS. However, heterozygous *NBN* pathogenic variants may be associated with an increased risk for breast cancer in women and prostate cancer in men. Carrier testing for at-risk family members and prenatal and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Nijmegen breakage syndrome (NBS) **should be suspected** in individuals with the following clinical and supportive laboratory findings.

Clinical features

- Disproportionate microcephaly that is progressive
- Craniofacial features that include a sloping forehead, upward-slanted palpebral fissures, prominent nose, relatively large ears, and retrognathia
- Growth deficiency that is more pronounced from birth until age two years, with mild improvement thereafter
- Recurrent infections including pneumonia, bronchitis, sinusitis, otitis media, and mastoiditis
- Malignancies, predominantly of lymphoid origin
- Decline in intellectual ability, from normal or borderline-normal during early childhood to moderate intellectual disability in older individuals

Supportive laboratory findings

- **Immunodeficiency** involving the humoral and cellular systems [Wolska-Kuśnierz et al 2015]:
    - The most frequent deficit was of IgG found in 62% of affected individuals and IgA deficiency in 57%.

- Deficiencies of IgG subclasses are frequent even when the IgG serum concentration is normal (IgG4, IgG2, and IgG3, in decreasing order).
- The most commonly reported defects in cellular immunity include reduced absolute numbers of total B cells (CD19+/CD20+), CD3+ T cells, and CD4+ T cells; these are observed in 80%-89% of affected individuals.
- The in vitro proliferation of T and B lymphocytes to antigen and/or mitogenic stimuli is moderately or severely reduced in majority of affected individuals, compared to age-matched healthy controls.

- **Chromosome instability**
  - Inversions and translocations involving chromosomes 7 and 14 are observed in PHA-stimulated lymphocytes in 10%-50% of metaphases.
  - The breakpoints most commonly involved are 7p13, 7q35, 14q11, and 14q32, which are the loci for immunoglobulin and T-cell receptor genes.

- **Radiation sensitivity.** Cells from individuals with NBS have a decrease in colony-forming ability following exposure to ionizing radiation and radiomimetics in vitro.

  Note: This test requires that a lymphoblastoid cell line be established. Because the process is more commonly performed in a research lab than in a clinical lab, the test may not be widely available clinically.

Establishing the Diagnosis

The diagnosis of NBS **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *NBN* identified by molecular genetic testing (see Table 1) and/or absent nibrin protein on an immunoblotting assay.

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants.

Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**.

- **Single-gene testing.** Targeted analysis for the common founder variant c.657_661del5 can be performed first. The c.657_661del5 pathogenic variant accounts for:
  - Approximately 100% of pathogenic alleles in individuals of Slavic (Poland, Czech Republic, Ukraine) ancestry;
  - More than 70% of pathogenic alleles in individuals from the US.

  If the common founder variant is not present in a homozygous form, sequence analysis of *NBN* can be pursued.

- **A multigene panel** that includes *NBN* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4)

Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Nijmegen Breakage Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
NBN	Targeted analysis for c.657_661del5 variant [3]	70%-100% [4]
	Sequence analysis [5]	~100%
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Methods that may be used to detect the c.657_661del5 pathogenic variant can include allele-specific PCR, sequence analysis, and genotyping assays designed to detect this variant. Note that these assays may not detect variants other than the targeted variant.
4. Nearly all affected individuals from Poland, the Czech Republic, and Ukraine tested to date are homozygous for the common pathogenic variant c.657_661del5. In a study of eight unrelated individuals with NBS from the Russian population, Resnick et al [2002] found that all but one of the 16 alleles were c.657_661del5. In the US, about 70% of individuals tested to date are homozygous for the common allele, 15% are heterozygous for c.657_661del5 and a second unique pathogenic variant, and 15% are homozygous for a unique pathogenic variant. Almost all affected individuals in the US who have the c.657_661del5 pathogenic variant are of known Eastern European ancestry.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No large exon or multiexon deletions or duplications involving this gene have been reported to cause NBS.

Immunoblotting

Immunoblotting can be used to determine if the nibrin protein is present or absent.

Note: Immunoblotting requires that a lymphoblastoid cell line be established. Because this process is more commonly performed in a research lab than in a clinical lab, the test may not be widely available clinically.

Clinical Characteristics

Clinical Description

Nijmegen breakage syndrome (NBS) is characterized by progressive microcephaly, growth deficiency that improves with age, recurrent sinopulmonary infections, an increased risk for lymphoma, and premature ovarian failure in females. Developmental milestones are attained at the usual time during the first year; however, borderline delays in development and hyperactivity may be observed in early childhood. Intellectual abilities tend to decline over time. Secondary malignancies including solid tumors have been reported in several individuals.

Table 2. Nijmegen Breakage Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Microcephaly	>99%	
Growth deficiency	Variable w/age	Growth deficiency in newborns, infants, & toddlers; growth improves w/age.

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Immunodeficiency	≥99%	
Malignancy	>60% by age 25 yrs	
Infertility	100% of females	Data are limited for males.

Growth. Children with NBS are generally born with weight below normal for gestational age and microcephaly (i.e., head circumference >2 SD below the mean for age and sex). Microcephaly progresses with age – in contrast to linear growth, which may improve with age, causing disproportionate head dimensions compared to the rest of the body. Microcephaly is occasionally masked by hydrocephaly or developmental abnormalities of the brain [Szczałuba et al 2012].

Growth deficiency in the first years of life results in length/height that is usually below the third centile by age two years. Thereafter, linear growth velocity tends to normalize; however, many individuals remain shorter than their peers (i.e., affected individuals do not experience catch-up growth). Some adults, both females and males, can achieve height within lower-normal ranges [Chrzanowska et al 2012].

Craniofacial features. The craniofacial features discussed in Suggestive Findings are found in the majority of affected individuals and become more pronounced with age as microcephaly progresses.

Infections. Respiratory infections are the most common; recurrent pneumonia and bronchitis may result in bronchiectasis, and even in pulmonary failure and early death. Chronic diarrhea and urinary tract infections may also occur. The spectrum and frequency of infections and autoimmune complications in a large group of individuals with NBS was reported by Wolska-Kuśnierz et al [2015]. Correlation of the severity of respiratory tract infections with some humoral and cellular immune parameters was also presented. Most respiratory tract infections were caused by community-acquired pathogens; only about 5% of individuals suffered from opportunistic infections [Wolska-Kuśnierz et al 2015]. Another study showed low frequency of protective IgG antibodies to HBsAg after vaccination with Engerix-B®, indicating a very weak specific response [Gregorek et al 2002].

Buchbinder et al [2019] reported the presence of rubella-positive cutaneous and visceral granulomas following rubella vaccination in individuals with NBS. One individual with NBS had pulmonary granulomas with no evidence of an infectious pathogen or any manifestations of systemic granulomatosis of lymphoid malignancy [Marczak et al 2018].

Malignancy. According to Chrzanowska et al [2012], 40% of affected individuals reported to date have developed malignancies before age 20 years. Malignancies are primarily lymphomas [Gładkowska-Dura et al 2008, Wolska-Kuśnierz et al 2015]. Approximately 45% of lymphomas are of B-cell origin and 55% are T-cell lymphomas. Although complete clinical remission (for >5 years) can be successfully achieved, in a proportion of affected individuals outcome is complicated by relapse or the development of a second malignancy [Dembowska-Baginska et al 2009, Bienemann et al 2011].

Several children have developed solid tumors, including medulloblastomas, glioma, rhabdomyosarcomas, and bilateral ovarian germ cell tumor (in a female) [Chrzanowska et al 1997, Hiel et al 2001, Bakhshi et al 2003, Distel et al 2003, Meyer et al 2004, Sharapova et al 2021, Krawczyk et al 2022]. Radiotherapy of central nervous system tumors (medulloblastoma) caused severe complications and death in three individuals with NBS [Chrzanowska et al 1997, Bakhshi et al 2003, Distel et al 2003].

A recent study of 241 individuals with NBS showed improved long-term survival in those treated with hematopoietic stem cell transplantation (HSCT) during first malignancy remission [Wolska-Kusnierz et al 2021]. In a second study of 136 individuals with NBS – 62 of whom developed malignancies – seven individuals

were treated with HSCT due to leukemia/lymphoma; six, who were cancer-free, were transplanted due to immunodeficiency [Sharapova et al 2021].

Psychomotor and intellectual development. Developmental milestones are attained at the usual time during the first year. Normal or borderline intellectual development and psychomotor hyperactivity may be observed in early childhood / preschool age. Intellectual abilities tend to decline, with mild-to-moderate intellectual disability during childhood. Affected children are described as having a cheerful, shy personality with good interpersonal skills.

Fertility. Results of a longitudinal study demonstrated the presence of hypergonadotropic hypogonadism in a large cohort of affected females, all of whom were homozygous for the common c.657_661del5 pathogenic variant [Chrzanowska et al 2010a].

No detailed studies of fertility in males with NBS have been published; however, puberty initiation and progress are comparable to healthy boys [Chrzanowska et al 2010b]. Warcoin et al [2009] described two adult sibs, a male with oligo-terato-asthenozoospermia and a female with premature ovarian failure, who had biallelic truncating variants in *NBN* but none of the other clinical features of NBS.

Other findings

- Irregular skin pigmentation in the form of irregular hyperpigmented or hypopigmented macules is seen in most affected individuals. In some affected individuals, progressive sarcoid-like granulomas are observed [Yoo et al 2008, Pasic et al 2012].
- Congenital malformations, usually observed in single cases, include anomalies of the central nervous system (e.g., hydrocephaly, schizencephaly, arachnoid cysts), choanal atresia, cleft lip and palate, tracheal hypoplasia, preaxial or postaxial polydactyly, horseshoe kidney, hydronephrosis, hypospadias, anal stenosis/atresia, and congenital hip dysplasia.

Heterozygotes

An increased frequency of *NBN* pathogenic variant c.657_661del5 has been observed in individuals with several different cancers, including breast cancer, prostate cancer, medulloblastoma, and melanoma, suggesting that *NBN* pathogenic variants could play a role in the etiology of these types of cancer [Cybulski et al 2004, Steffen et al 2004, Ciara et al 2010].

Genotype-Phenotype Correlations

The common pathogenic variant c.657_661del5 and most other loss-of-function variants result in typical features of NBS. However, exceptions have been reported. There are two reports of families in which biallelic truncating variants in *NBN* occur in individuals with milder features:

- Varon et al [2006] described a woman age 53 years with NBS who was homozygous for the *NBN* truncating allele c.741_742dupGG. She had a somewhat milder phenotype, including microcephaly, chromosome instability, immunodeficiency, and primary amenorrhea. (Her sister, with similar clinical manifestations, had died at age 20 years of malignant lymphoma [Maraschio et al 1986]). However, analysis of transcripts from the woman's cells indicated a highly prevalent alternatively spliced form of *NBN* lacking exons 6 and 7 (where the pathogenic variant is located). This transcript codes for a 73-kd form of NBN with an internal deletion.
- Warcoin et al [2009] described a family in which two healthy adult sibs, a sister and brother, had biallelic truncating variants in *NBN* (p.Tyr110Ter and p.Trp375Ter). Neither sib had short stature, reduced head circumference, or dysmorphic facial features; however, both were referred for fertility defects (premature ovarian failure and oligo-terato-asthenozoospermia) and were subsequently found to have the cellular

phenotypes typical of NBS, including chromosome instability, hypersensitivity to ionizing radiation, and impaired checkpoint responses.

Nomenclature

The Nijmegen breakage syndrome (NBS) was described by Weemaes et al [1981].

Three Czech families with Seemanová syndrome [Seemanová et al 1985] were later identified as having NBS.

Prevalence

No reliable estimates of worldwide prevalence exist, but it is likely to approximate 1:100,000 live births.

NBS is most common in Eastern European / Slavic populations. Studies in Poland, the Czech Republic, and Ukraine have suggested that the carrier frequency of the common allele approaches 1:155 in these populations [Varon et al 2000, Seemanová et al 2004]. The highest reported prevalence is in the Sorbian population, an isolated Slavic group from southeastern Germany, in whom the carrier frequency is estimated at 1:34 [Maurer et al 2010]. In a cohort of 136 individuals with NBS from Belarus, Ukraine, Russia, and Latvia, the highest prevalence was found in Belarus and Ukraine (2.3 and 1.3 in 1 million, respectively), with the highest incidence in western Belarus and western Ukraine (>2:100,000) [Sharapova et al 2021].

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *NBN*.

Differential Diagnosis

Microcephaly, growth delay, immunodeficiency, and/or bone marrow failure are common manifestations of several inherited disorders, mainly related to defective sensing, processing, and repair of double-strand DNA breaks. Recurrent infections, poor growth, and immunodeficiency can be observed in other inherited immunodeficiencies. See Table 3.

The early growth failure in Nijmegen breakage syndrome (NBS) may suggest other disorders of growth, such as thyroid hormone or growth hormone deficiency, or primary disorders of bone growth (e.g., skeletal dysplasias).

Because malignancy may be the presenting finding in NBS, the diagnosis of NBS should be considered before radiotherapy is initiated in individuals with microcephaly who have solid tumors and are younger than age three years [Bakhshi et al 2003, Distel et al 2003, Meyer et al 2004].

Table 3. Disorders to Consider in the Differential Diagnosis of Nijmegen Breakage Syndrome

Gene(s)	Disease Name	Immunodeficiency &/or Bone Marrow Failure	Microcephaly / Craniofacial Features	Growth Delay	Cellular Sensitivity	Chromosome Instability	Cancer Predisposition	Other
NBN	Nijmegen breakage syndrome (NBS; topic of this chapter)	Immunodeficiency, combined; recurrent sinopulmonary infections	Progressive disproportionate microcephaly; characteristic facial features [1]	Mild growth restriction	↓ in colony-forming ability after exposure to ionizing radiation & radiomimetics	Inversions & translocations involving chromosomes 7 & 14 in lymphocytes	↑ risk, mainly of lymphoid origin	Primary ovarian failure; mild-to-moderate ID
BRCA1 *BRCA2* *BRIP1* *ERCC4* *FAAP100* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* *FANCL* *FANCM* *MAD2L2* *PALB2* *RAD51* *RAD51C* *RFWD3* *SLX4* *UBE2T* *XRCC2*	Fanconi anemia	Progressive bone marrow failure (pancytopenia); myelodysplastic syndrome	Microcephaly (1/3 of persons)	Growth restriction	Cellular sensitivity to ionizing radiation & DNA cross-linking agents [2]	Chromosome breakage induced by mitomycin C & diepoxybutane [2]	Myeloblastic leukemia; solid tumors	Limited fertility
CREBBP *EP300*	Rubinstein-Taybi syndrome	Recurrent infections; defect in polysaccharide antibody response	Microcephaly; distinctive facial features	Mild growth restriction; short stature	No cellular sensitivity	Not present	Leukemia; tumors that affect head	ID

Table 3. continued from previous page.

Gene(s)	Disease Name	Immunodeficiency &/or Bone Marrow Failure	Microcephaly / Craniofacial Features	Growth Delay	Cellular Sensitivity	Chromosome Instability	Cancer Predisposition	Other
LIG4	*LIG4* syndrome [3] (OMIM 606593)	Immunodeficiency, combined; pancytopenia & myelodysplastic syndrome	Microcephaly; facial features resembling NBS [1]	Short stature	Severe radiosensitivity	↑ chromosome breakage rate	Predisposition to malignancy (mainly lymphoma & leukemia)	High intrafamilial clinical variability
NHEJ1	*NHEJ1* syndrome (Cernunnos-XLF deficiency) (OMIM 611291)	Mild immunodeficiency to severe combined immunodeficiency	Microcephaly	Severe (typically) growth restriction	Cellular sensitivity to ionizing radiation	High chromosome breakage rate (w/o chromosome 7;14 rearrangements) [4]	Limited data; unknown	
RAD50	Nijmegen breakage syndrome-like disorder (RAD50 deficiency) (OMIM 613078)	No immunodeficiency reported	Microcephaly; facial features resembling NBS [1]	Severe growth restriction	X-ray hypersensitivity	Chromosome instability (incl 7;14 rearrangements) in lymphocytes & fibroblasts	Limited data; unknown	Normal puberty; disturbed sensorimotor coordination; ID
ATR *CENPJ* *CEP152* *CEP63* *DNA2* *NIN* *NSMCE2* *RBBP8* TRAIP	Seckel syndrome (OMIM PS210600)	Pancytopenia	Severe microcephaly	Severe growth restriction	Not typically radiosensitive by colony survival assay [5]	↑ sister chromatid exchange	Limited data, possible myelodysplasia	ID
XRCC4 [6]	Short stature, microcephaly, & endocrine dysfunction (OMIM 616541)	No clinical manifestations of immunodeficiency	Primary microcephaly	Severe growth restriction	Pronounced cellular radiosensitivity	Not reported	Solid tumor	Primary ovarian failure; early-onset metabolic syndrome

ID = intellectual disability

1. Facial features characteristic of Nijmegen breakage syndrome are a sloping forehead, retrognathia, prominent nasal bridge and nose, large ears, and upslanted palpebral fissures.

2. Increased sensitivity of lymphocytes to alkylating agents such as mitomycin C and/or diepoxybutane is the cellular marker of Fanconi anemia and is used as a diagnostic aid.

3. Altmann & Gennery [2016], Felgentreff et al [2016]

4. Dutrannoy et al [2010]

5. O'Driscoll et al [2003]

6. XRCC4 is another component of the nonhomologous end joining (NHEJ) pathway.

Management

No clinical practice guidelines for Nijmegen breakage syndrome (NBS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with NBS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Nijmegen Breakage Syndrome

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth & nutrition	
Immunology	• Eval of immunologic profile at time of diagnosis • Assessment of types & frequency of infections • Absolute number of B cells, T cells, & T-cell subsets, w/special attention to naïve CD4+CD45RA cells • Proliferative response of peripheral blood mononuclear cells to stimuli • Concentration of total serum immunoglobulins (IgG, IgA, IgM) & IgG subclasses • Eval for viruses w/lymphotropic capacity (i.e., EBV, CMV)	
Pulmonary	Assess pulmonary function in those w/recurrent/chronic pulmonary infections.	
Malignancy	• Assess for signs/symptoms of lymphoma & solid tumors. • Assess family history for malignancy.	
Endocrine	• Eval by gynecologist &/or endocrinologist • Pelvic ultrasound to evaluate for streak gonads • Plasma FSH, LH, & estrogen	In females of pubertal age
Neurodevelopment	Assess cognitive development & intellectual abilities.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of NBS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CMV = cytomegalovirus; EBV = Epstein-Barr virus; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOI = mode of inheritance; NBS = Nijmegen breakage syndrome

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Nijmegen Breakage Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Immunodeficiency	Antibiotics as needed for infections; selected for microorganism being treated	The spectrum of recurrent infections in NBS is not opportunistic. Long-term antibiotic, antiviral, or antifungal prophylaxis is not recommended.
	Consider Ig replacement, typically intravenously (IVIg) or subcutaneously (SCIg).	In those w/severe hypogammaglobulinemia & frequent infections
	Acellular vaccines are recommended.	Live vaccines (against tuberculosis, measles, mumps, rubella, & varicella) should not be given.
Pulmonary infections	• Standard treatments for bronchiectasis • Treatment of pulmonary infection is based on underlying pathogen.	
Malignancy	• Lymphoid malignancy • Chemotherapy protocols need to be adapted to individual tolerance. [1] • Requires careful follow up by oncologist, as symptoms of lymphoid malignancies in immunodeficient persons can be misleading.	• There are currently no dedicated protocols of cancer treatment for persons w/NBS or recommendations of chemotherapy reduction. • Notably, ↓ chemotherapy dosages were not assoc w/↓ side effects but contributed to ↑ risk of disease recurrence & poorer overall survival.
	Treatment of solid tumors depends on type of malignancy.	• Protocols should be adapted for NBS depending on treatment tolerance. • Radiotherapy & radiomimetic chemotherapeutics are avoided.
	Consider HSCT.	Recommended after 1st remission from malignancy of hematologic origin [2]
Hypergonadotropic hypogonadism	• Consider HRT. • Careful monitoring of secondary sexual characteristics & uterus development is needed.	HRT is recommended at appropriate age to induce secondary sexual characteristics & to prevent osteoporosis & metabolic, cardiovascular, & psychosocial sequelae.

HRT = hormonal replacement therapy; HSCT = hematopoietic stem cell transplantation
1. Dembowska-Baginska et al [2009], Pastorczak et al [2016]
2. Wolska-Kusnierz et al [2021]

Surveillance

Table 6. Recommended Surveillance for Individuals with Individuals with Nijmegen Breakage Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Monitor weight, length/height, & head circumference.	Monthly until age 1 yr; every 3-6 mos until age 2-3 yrs; annually thereafter
Immunology	• Monitor types & frequency of infections. • Absolute number of B cells, T cells, & T-cell subsets, w/ special attention to naïve CD4+CD45RA cells • Proliferative response of peripheral blood mononuclear cells to stimuli • Concentration of total serum immunoglobulins (IgG, IgA, IgM) & IgG subclasses • Eval for viruses w/lymphotropic capacity (i.e., EBV, CMV)	• Eval of cellular immunity & proliferative response to mitogens or antigens every 12 mos • Eval of humoral immunity parameters every 6 wks until age 1 yr, then every 3-6 mos (until IVIg therapy is started) • Periodic quantitative monitoring of indicators of viral infections 1x/yr or when infection is suspected

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Malignancy	• Monitor for malignancy, particularly in those w/weight loss, fever, weakness, enlargement of peripheral lymph nodes, dyspnea, cough, &/or hepatosplenomegaly. • Assessment should be considered using ultrasonography, MRI, biopsy.	Annually
	Breast self-exam	Monthly in females when HRT is administered.
Endocrine	• Monitor pubertal progression in females & males. • Assess for premature ovarian insufficiency in females.	
Neurodevelopment	Assess cognitive development & intellectual abilities.	Before starting school & repeated periodically to ensure educational support as needed

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HRT = hormonal replacement therapy

Carriers (heterozygotes)

- **Parents.** As obligate carriers, parents should be monitored for malignancy, in particular breast cancer in women and prostate cancer in men. No consensus tumor screening protocols for carriers have been published.
- **At-risk sibs.** Evidence of cancer risk in young carriers is insufficient to warrant screening in childhood.

Agents/Circumstances to Avoid

Because the cells from individuals with NBS are as radiosensitive in vitro as those from individuals with ataxia-telangiectasia (another chromosome instability syndrome), conventional doses of radiation used in radiotherapy could be lethal in individuals with NBS. Family members should be made aware of the risk associated with radiotherapy so that they can discuss appropriate treatment options if a malignancy is diagnosed.

Similarly, unnecessary exposure to ionizing radiation should be avoided; instead of radiograph or CT scan, MRI and/or ultrasound examination are strongly recommended.

Live vaccines (e.g., live vaccines for tuberculosis, measles, mumps, rubella, and varicella) should not be given.

Evaluation of Relatives at Risk

It is appropriate to offer molecular genetic testing for the *NBN* pathogenic variants identified in the proband to apparently asymptomatic adult relatives of an affected individual in order to identify family members who are heterozygous for an *NBN* pathogenic variant and would benefit from monitoring for malignancy (see Clinical Description, Heterozygotes and Surveillance, **Carriers**).

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

Nijmegen breakage syndrome (NBS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *NBN* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *NBN* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are not at risk for NBS; however, in some populations, there is clear evidence of increased cancer risk among individuals heterozygous for an *NBN* pathogenic variant (e.g., c.657_661del5) (see Clinical Description, Heterozygotes). Heterozygous parents should be monitored for malignancy, particularly breast cancer in women and prostate cancer in men (see Surveillance).

Sibs of a proband

- If both parents are known to be heterozygous for an *NBN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and having NBS, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *NBN* pathogenic variants.
- Heterozygotes are not at risk for NBS; however, in some populations there is clear evidence of increased cancer risk among individuals heterozygous for an *NBN* pathogenic variant (e.g., c.657_661del5) (see Clinical Description, Heterozygotes). Adult heterozygous sibs should be monitored for malignancy, particularly breast cancer in women and prostate cancer in men (see Surveillance).

Offspring of a proband. To date, individuals with NBS are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *NBN* pathogenic variant and at increased risk for malignancy (see Clinical Description, Heterozygotes).

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *NBN* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *NBN* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for NBS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MedlinePlus**
  Nijmegen breakage syndrome
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry

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. Nijmegen Breakage Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NBN	8q21.3	Nibrin	NBN @ LOVD	NBN	NBN

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 Nijmegen Breakage Syndrome (View All in OMIM)

251260	NIJMEGEN BREAKAGE SYNDROME; NBS
602667	NIBRIN; NBN

Molecular Pathogenesis

NBN encodes nibrin, also known as p95. Nibrin is ubiquitously expressed. There is no sequence homology between nibrin and other known proteins. However, nibrin contains a forkhead-associated domain and two breast cancer carboxy-terminal domains, which are involved in cellular responses to DNA damage. In normal fibroblasts, nibrin is associated with two other proteins involved in DNA repair, hMre11 and hRad50. On exposure to ionizing radiation, the associated proteins hMre11, hRad50, and nibrin form nuclear foci at sites where DNA repair has taken place. Nibrin targets the *NBN*/Mre11/Rad50 complex to sites of double-strand

breaks and interacts with ATM kinase to coordinate cell cycle arrest with DNA repair [Carney et al 1998, Matsuura et al 2004, Falck et al 2005].

Most known *NBN* pathogenic variants are predicted to result in truncation of the nibrin protein. All known NBS-related pathogenic variants occur in exons 6-10; presumably reflecting a requirement for production of a C-terminal protein fragment of nibrin that occurs by translational reinitiation mechanism [Maser et al 2001]. The requirement that protein termination and reinitiation occur in the same reading frame potentially limits the pathogenic variants that can give rise to NBS.

Mechanism of disease causation. Loss of function

Table 7. Notable *NBN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [References]
NM_002485.5 NP_002476.2	c.330T>G	p.Tyr110Ter	See Genotype-Phenotype Correlations.
	c.643C>T	p.Arg215Trp	Reported in MZ twins also heterozygous for c.657_661del5 w/more severe neurologic features but w/o cellular & radiation sensitivity [Seemanová et al 2006]
	c.657_661delACAAA (c.657_661del5; 657del5)	p.Lys219AsnfsTer16	Slavic founder variant [Varon et al 1998]
	c.741_742dupGG (742insGG)	p.Glu248GlyfsTer5	See Genotype-Phenotype Correlations.
	c.1089C>A	p.Tyr363Ter	Homozygous in affected persons from 1 family w/ features of atypical Fanconi anemia [Gennery et al 2005, New et al 2005]
	c.1125G>A	p.Trp375Ter	See Genotype-Phenotype Correlations.

MZ = monozygotic
Variants listed in the table have been provided by the authors. *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.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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- 30 November 2023 (sw/aa) Revision: added information about cancer surveillance for heterozygotes in Evaluation of Relatives at Risk; deleted *ATM* from Differential Diagnosis
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- 1 March 2011 (me) Comprehensive update posted live
- 14 June 2005 (me) Comprehensive update posted live
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- 17 May 1999 (me) Review posted live
- 5 January 1999 (pc) Original submission

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