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ALK-Related Neuroblastic Tumor Susceptibility

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Summary

Clinical characteristics

ALK-related neuroblastic tumor susceptibility is characterized by increased risk for neuroblastic tumors including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas. Neuroblastomas are a more malignant tumor and ganglioneuromas a more benign tumor. Depending on the histologic findings, ganglioneuroblastomas can behave in a more aggressive fashion, like neuroblastomas, or in a benign fashion, like ganglioneuromas. The overall penetrance of a germline *ALK* pathogenic variant is approximately 50%, with the risk for neuroblastic tumor development highest in infancy and decreasing by late childhood.

Diagnosis/testing

ALK-related neuroblastic tumor susceptibility is established by identification of a heterozygous germline *ALK* activating pathogenic variant in the tyrosine kinase domain that is known or suspected to cause altered kinase function by molecular genetic testing.

Management

Treatment of manifestations: Children who develop neuroblastic tumors should be evaluated and treated by a pediatric oncologist at a pediatric cancer center. Treatment for individuals with neuroblastomas and ganglioneuroblastomas who have a germline *ALK* activating pathogenic variant is the same standard risk-stratified therapy used to treat all neuroblastoma. Ganglioneuromas are typically removed by surgical resection and require no further therapy.

Surveillance: In asymptomatic children and after successful treatment of neuroblastic tumors: abdominal ultrasound and urine catecholamine metabolite levels (homovanillic acid and vanillylmandelic acid) every three months and physical examination and chest radiograph every six months between birth and age six years; physical examination, abdominal ultrasound, and measurement of urine catecholamine metabolite levels every

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six months and chest radiograph every six to 12 months between ages six and ten years. Screening beyond age ten years is not indicated.

Evaluation of relatives at risk: It is appropriate to test relatives at risk (e.g., sibs age <10 years at the time of diagnosis of the proband, as well as sibs born subsequently) for the *ALK* pathogenic variant found in the proband to identify those for whom early detection of neuroblastomas and initiation of therapy would likely improve quality of life and possibly affect outcome (if therapy is started prior to end organ damage).

Genetic counseling

ALK-related neuroblastic tumor susceptibility is inherited in an autosomal dominant manner. Some individuals diagnosed with *ALK*-related neuroblastic susceptibility inherited a pathogenic variant from a heterozygous parent. Because of reduced penetrance, a parent may have a germline *ALK* activating pathogenic variant without having developed a neuroblastic tumor. Some individuals diagnosed with *ALK*-related neuroblastic tumor susceptibility have the disorder as the result of a *de novo* germline activating pathogenic variant; the proportion of probands who have a *de novo* pathogenic variant is unknown. Each child of an individual with *ALK*-related neuroblastic tumor susceptibility has a 50% chance of inheriting the *ALK* pathogenic variant. The likelihood that a child who inherits the pathogenic variant will develop a neuroblastic tumor is unknown, though the penetrance is estimated to be around 50%. Once the germline *ALK* activating pathogenic variant has been identified in an affected family member, genetic testing of at-risk asymptomatic relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

ALK-Related Neuroblastic Tumor Susceptibility: Included Phenotypes [1]
• Neuroblastoma • Ganglioneuroblastoma • Ganglioneuroma

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

ALK-related neuroblastic tumor susceptibility **should be suspected** in probands with:

- A neuroblastic tumor including neuroblastoma, ganglioneuroblastoma, or ganglioneuroma;
- Multiple primary neuroblastic tumors that arise either synchronously or metachronously;
- A family history of one or more relatives with one of these three neuroblastic tumors. Note: Both benign and malignant tumors can occur in the same family.

As neuroblastoma most often occurs sporadically and is rarely attributed to germline variants in cancer-predisposing genes (1%-2% of individuals), routine germline testing for *ALK* pathogenic variants is not standard. However, considerations for testing for germline *ALK* pathogenic variants include the following strong and moderate recommendations [Bourdeaut et al 2012; Brodeur et al 2017; Kamihara et al, unpublished data].

Recommendations for Testing for Germline *ALK* Pathogenic Variants

Strong recommendation

- All children with documented somatic *ALK* pathogenic variants within a neuroblastic tumor

- An individual with a neuroblastic tumor* who has at least one first-degree relative with a neuroblastic tumor

  * Germline *ALK* pathogenic variants are equally likely to be identified in individuals with any of the three neuroblastic tumor types and with any stage of malignant neuroblastoma [Liu & Thiele 2012].

- An individual with a neuroblastic tumor and a family history of neuroblastic tumors that are not a manifestation of a neural crest disorder such as Hirschsprung disease or central hypoventilation syndrome, which may suggest pathogenic variants in *PHOX2B* (See Differential Diagnosis.)

Moderate recommendation. A simplex case (i.e., a single occurrence in a family) with bilateral neuroblastoma or multifocal primary neuroblastic tumors [Bourdeaut et al 2012]

No recommendation. An individual with a neuroblastic tumor and distant relatives (≥2nd degree) with a history of neuroblastic tumors, as such an individual is unlikely to have a germline *ALK* pathogenic variant [Mossé et al 2008]

Considerations for Testing for Somatic *ALK* Pathogenic Variants

Some institutions are currently screening tumors of all children with neuroblastoma, and others are screening tumors at the time of recurrence or progression, primarily for potential for *ALK*-directed therapy (see Molecular Genetics, Cancer and Benign Tumors), rather than identifying those at increased risk of having a germline *ALK* pathogenic variant.

Establishing the Diagnosis

The diagnosis of *ALK*-related neuroblastic tumor susceptibility **is established** in a proband by identification of a heterozygous germline *ALK* activating pathogenic (or likely pathogenic) variant in the tyrosine kinase domain that is known or suspected to cause altered kinase function by molecular genetic testing (see Table 1).

Note: (1) 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 likely pathogenic variants. (2) Identification of a heterozygous *ALK* variant of uncertain significance does not establish or rule out the diagnosis.

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

- **Single-gene testing.** Sequence analysis of *ALK* may detect heterozygous germline activating pathogenic variants in the tyrosine kinase domain that are known or suspected to cause altered kinase function.

  Note: *ALK*-related neuroblastic tumor susceptibility is postulated to occur through a gain-of-function mechanism. Large intragenic deletion or duplication has not been reported; testing for intragenic deletions or duplication is not indicated.

- **A multigene panel** that includes *ALK* and other genes of interest (see Differential Diagnosis) may be considered 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. 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*. (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 *ALK*-Related Neuroblastic Tumor Susceptibility

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ALK	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported

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. 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.
4. In families with two or more first-degree relatives with neuroblastoma, the incidence of germline *ALK* pathogenic variants is 80%. In families in which two second-degree or more distant relatives have neuroblastoma, the incidence of germline *ALK* pathogenic variants is much lower [Mossé et al 2008].
5. Somatic *ALK* activating pathogenic variants, which may be found in 7%-8% of sporadic neuroblastoma tumors, are rarely associated with germline *ALK* pathogenic variants [Liu & Thiele 2012]. In 167 tumors tested from simplex cases with high-risk neuroblastomas, Mossé et al [2008] found that 14 had somatic *ALK* missense variants that were predicted to be activating. Of these 14 individuals with somatic *ALK* missense variants, germline DNA was available on nine. In one of those nine individuals the *ALK* pathogenic variant was identified in both germline and tumor DNA.
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.

Clinical Characteristics

Clinical Description

Individuals with *ALK*-related neuroblastic tumor susceptibility are at risk of developing a spectrum of neuroblastic tumors that include neuroblastomas, ganglioneuroblastomas, and ganglioneuromas. These individuals also have a higher-than-average incidence of other primary tumors (e.g., bilateral adrenal tumors, extra-adrenal tumors arising at sites of sympathetic ganglions).

Neuroblastic tumors. Risk for neuroblastic tumor development is highest in infancy and decreases by late childhood, with 98% of neuroblastic tumors occurring by age ten years [Brodeur et al 2017]. Individuals with familial neuroblastoma tend to develop tumors at a younger age (average age nine months) than those without familial predisposition (age two to three years) [Park et al 2008]. One study showed that 45%-50% of individuals with a germline *ALK* pathogenic variant will develop a neuroblastic tumor in their lifetime [Brodeur et al 2017].

Within this spectrum, neuroblastomas represent a more malignant tumor and ganglioneuromas a more benign tumor. The three neuroblastic tumor types are defined histologically. Depending on the histologic findings, ganglioneuroblastomas can behave in a benign fashion, like ganglioneuromas, or in a more aggressive fashion, like neuroblastomas.

Multiple primary tumors. Individuals with familial neuroblastomas also have a higher-than-average incidence of multiple primary tumors [Mossé et al 2008, Park et al 2008]. The multiple primary tumors may be bilateral adrenal tumors or multiple primary extra-adrenal tumors arising at sites of sympathetic ganglions. The tumors can occur either synchronously or metachronously [Bourdeaut et al 2012].

Non-neuroblastic tumors. There have been rare case reports of germline *ALK* variants identified in individuals with tumors outside of the neuroblastic family. Twelve individuals with glioma had a germline *ALK* variant [Bu

et al 2021]. Only one of these variants occurred in the tyrosine kinase domain and was a nonsense variant. All other variants were missense. There were no recurrent germline variants, and somatic mutation of the second allele was not investigated, so causality of germline *ALK* variants in glioma has not been established. *ALK* germline variants have also been identified, rarely, in individuals with medulloblastoma [Jovanović et al 2023]. There is currently not enough evidence to say that individuals with germline *ALK* variants are at increased risk for primary central nervous system tumors.

Outcome. Given the rarity of familial neuroblastic tumors, statistically significant long-term outcome data are not yet available for individuals with *ALK*-related neuroblastic tumor susceptibility. Although long-term survivors of neuroblastomas who are heterozygous for an inherited germline *ALK* pathogenic variant have been reported [Carén et al 2008], no prospective studies have evaluated the survival of persons with a germline *ALK* pathogenic variant compared to those with neuroblastomas not associated with a germline *ALK* pathogenic variant.

Since neuroblastomic tumor outcome is heavily dependent on biological characteristics and stage of the tumor, it is likely that survival from a neuroblastic tumor depends more on tumor type (neuroblastomas having the poorest outcome), tumor stage, and appropriate medical intervention than on the presence or absence of a germline *ALK* activating pathogenic variant [Park et al 2008].

Genotype-Phenotype Correlations

Aside from the following pathogenic variants, no associations between specific germline *ALK* pathogenic variants and risk of developing neuroblastomas or outcome of neuroblastomas have been established [Azarova et al 2011].

The pathogenic variant p.Arg1275Gln, found in approximately 45% of individuals with a germline *ALK* pathogenic variant [Wood et al 2009], may be associated with somewhat decreased penetrance (40%).

The pathogenic variant p.Gly1128Ala, reported as a germline *ALK* pathogenic variant in one large family, appeared to have lower penetrance: 40% of heterozygotes developed a neuroblastoma during childhood [Mossé et al 2008]. Adult heterozygotes were healthy; no tumor types other than neuroblastoma were reported.

Penetrance

The overall penetrance of a germline *ALK* pathogenic variant is approximately 50% [Brodeur et al 2017]. Several obligate heterozygous asymptomatic adults have been identified [Mossé et al 2008, Bourdeaut et al 2012]. In at least one family, a child with neuroblastoma inherited the p.Arg1275Gln pathogenic variant from an unaffected father [Mossé et al 2008].

See also Genotype-Phenotype Correlations for information on penetrance.

Prevalence

Familial neuroblastoma occurs in approximately 1%-2% of all individuals with neuroblastoma [Weiss et al 2016]. Of those familial cases, gain-of-function pathogenic variants in *ALK* account for 75% [Ritenour et al 2018].

Genetically Related (Allelic) Disorders

Germline *ALK* pathogenic variants. The majority of individuals with a germline *ALK* pathogenic variant have no obvious phenotype other than predisposition to neuroblastoma. The exceptions are the pathogenic variants p.Phe1174Val and p.Phe1245Val, identified in the germline in two unrelated children with congenital neuroblastoma, severe developmental delay, and structural brain stem abnormalities. Although these pathogenic

variants have been reported as somatic variants in neuroblastoma tumors, they have not been reported in the germline of phenotypically normal individuals with neuroblastoma [de Pontual et al 2011].

Sporadic tumors (including neuroblastomas) occurring as single tumors in the absence of any other findings of this syndrome frequently contain a somatic pathogenic variant in *ALK* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Germline pathogenic variants in *ALK* and *PHOX2B* are the etiologic agents for familial neuroblastoma susceptibility.

- Heterozygous germline *ALK* pathogenic variants are the main cause of familial susceptibility to neuroblastoma in otherwise healthy individuals.
- Heterozygous germline *PHOX2B* pathogenic variants account for the remainder of families, most of whom also have disorders of neural crest development [Mossé et al 2008, Azarova et al 2011].

PHOX2B-related neuroblastoma susceptibility and other disorders to consider in the differential diagnosis of *ALK*-related neuroblastic tumor susceptibility are summarized in Table 2.

Table 2. Neuroblastoma Susceptibility Disorders to Consider in the Differential Diagnosis of *ALK*-Related Neuroblastic Tumor Susceptibility

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/*ALK*-NTS	Distinguishing from *ALK*-NTS
2p24 duplication (incl *MYCN* & *DDX1*)	Chromosome 2p24 duplication [1]	AD	Neuroblastoma	Wilms tumor
BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2*	Noonan syndrome	AD AR [2]	Neuroblastoma	• Characteristic facies • Short stature • Congenital heart disease • Developmental delay • Leukemias, rhabdomyosarcoma
EZH2	Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	Neuroblastoma	• Leukemia / non-Hodgkin lymphoma • Overgrowth • Characteristic facial features (broad forehead, ocular hypertelorism, long/prominent philtrum, "stuck-on" appearance of chin

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/*ALK*-NTS	Distinguishing from *ALK*-NTS
HRAS	Costello syndrome	AD	Neuroblastoma	• Characteristic facies • Growth deficiency • Developmental delay • Characteristic hair & skin findings • Cardiac disease
KIF1B	*KIF1B*-related neuroblastoma susceptibility (OMIM 256700)	AD	Neuroblastoma, ganglioneuroma	Pheochromocytomas, leiomyosarcoma
NF1	Neurofibromatosis 1	AD	Neuroblastoma	• Café au lait macules, intertriginous freckling, cutaneous neurofibromas • Peripheral nerve sheath tumors • Iris Lisch nodules • Learning disabilities &/or behavior issues
PHOX2B	*PHOX2B*-related familial neuroblastoma susceptibility (OMIM 613013)	AD	Familial neuroblastoma	• Hirschsprung disease • ↓ esophageal motility • Congenital central hypoventilation syndrome • Characteristic facial features (downslanted palpebral fissures, small nose, triangular mouth, low-set & posteriorly rotated ears)
TP53	Li-Fraumeni syndrome	AD	Neuroblastoma	Soft-tissue sarcomas, osteosarcoma, breast cancer, brain tumors, adrenocortical carcinoma, leukemias
Numerous mechanisms [3]	Beckwith-Wiedemann syndrome	See footnote 3.	Neuroblastoma	• Macrosomia, macroglossia, visceromegaly, omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, renal abnormalities, hemihyperplasia • Wilms tumor, hepatoblastoma, rhabdomyosarcoma

AD = autosomal dominant; *ALK*-NTS = *ALK*-related neuroblastic tumor susceptibility; AR = autosomal recessive; MOI = mode of inheritance

1. Williams et al [2015]

2. Noonan syndrome is most often inherited in an autosomal dominant manner. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

3. Beckwith-Wiedemann syndrome (BWS) is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5 (also known as the BWS critical region). Regulation may be disrupted by any one of numerous mechanisms (see Beckwith-Wiedemann Syndrome, Molecular Pathogenesis). Reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region. The majority of families have a recurrence risk of less than 1%.

Neuroblastoma susceptibility candidate genes include *SMARCA4* [Witkowski et al 2023] and *BARD1* [Kim et al 2024].

*R*apid-onset *o*besity with *h*ypothalamic dysfunction, *h*ypoventilation, *a*utonomic *d*ysregulation, and *ne*ural crest *t*umor, also called ROHHAD(NET) syndrome – a disorder of unknown genetic cause – can also be considered in the differential diagnosis. Like *ALK*-related neuroblastic tumor susceptibility, ROHHAD(NET) syndrome is associated with ganglioneuroblastomas and ganglioneuromas. ROHHAD(NET) syndrome can be distinguished by the presence of rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation [Harvengt et al 2020].

Management

No clinical practice guidelines for *ALK*-related neuroblastic tumor susceptibility have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ALK*-related neuroblastic tumor susceptibility, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. *ALK*-Related Neuroblastic Tumor Susceptibility: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neuroblastic tumors	Physical exam to assess for clinical manifestations of neuroblastic tumors (e.g., abdominal mass, Horner syndrome, &/or cutaneous lesions)	
	Chest radiograph & abdominal ultrasound	Chest & abdomen are the most common sites for neuroblastic tumor development.
	Measurement of urine catecholamine metabolite levels (homovanillic acid & vanillylmandelic acid)	May be ↑ in presence of neuroblastic tumor
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ALK*-NTS to facilitate medical & personal decision making

ALK-NTS = *ALK*-related neuroblastic tumor susceptibility; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The treatment for individuals with a neuroblastic tumor who have a germline *ALK* activating pathogenic variant is the same standard risk-stratified therapy used to treat all neuroblastic tumors. Children who develop neuroblastic tumors (neuroblastomas, ganglioneuroblastomas, or ganglioneuromas) should be evaluated and treated by a pediatric oncologist at a pediatric cancer center.

Table 4. *ALK*-Related Neuroblastic Tumor Susceptibility: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neuroblastoma & ganglioneuroblastoma	• Depending on age of affected person, tumor stage, & biologic characteristics, treatment may involve observation or surgical resection. • Tumors w/risk for metastatic spread or those that have already metastasized require chemotherapy & sometimes radiation therapy, HSCT, & immunotherapy.	• The mgmt guidelines for neuroblastomas & ganglioneuroblastomas are complex. [1] • Clinical trials are ongoing to study efficacy of *ALK*-targeted therapy in the setting of a new diagnosis (see Therapies Under Investigation). • *ALK*-targeted therapy in the setting of relapsed & refractory neuroblastomas & ganglioneuroblastomas has demonstrated improved response & spurred rapid translation into Phase III trials (see Therapies Under Investigation). [2]
Ganglioneuromas	Typically surgical resection w/o further therapy	

HSCT = hematopoietic stem cell transplantation
1. Irwin & Park [2015]
2. Goldsmith et al [2023]

Surveillance

Guidelines for the screening of asymptomatic children with familial neuroblastoma – including those with germline *ALK* activating pathogenic variants – were published in 2017 and are being updated [Brodeur et al 2017; Kamihara et al, unpublished data]. Surveillance is also recommended for children with a germline *ALK* activating pathogenic variant who were successfully treated for a neuroblastoma due to risk of developing multiple primary tumors.

Table 5. *ALK*-Related Neuroblastic Tumor Susceptibility: Recommended Surveillance

System/Concern	Age	Evaluation	Frequency
Neuroblastic tumors	Age 0-6 yrs	• Abdominal ultrasound • Measurement of urine catecholamine metabolite levels (homovanillic acid & vanillylmandelic acid)	Every 3 mos
		• Physical exam • Chest radiograph	Every 6 mos
	Age 6-10 yrs	• Physical exam • Abdominal ultrasound • Measurement of urine catecholamine metabolite levels (homovanillic acid & vanillylmandelic acid)	
		Chest radiograph	Every 6-12 mos
	Age >10 yrs	No screening recommended	

Agents/Circumstances to Avoid

There is currently no evidence that individuals with *ALK*-related neuroblastoma tumor susceptibility have increased sensitivity to chemotherapeutic agents or radiation therapy; thus, medical and surgical management of tumors should be the same as for the general population.

Evaluation of Relatives at Risk

It is appropriate to test sibs younger than age ten years at the time of the proband's diagnosis as well as sibs born subsequently for the *ALK* pathogenic variant found in the proband. Genetic testing identifies sibs at high risk for

neuroblastoma, for whom early detection of neuroblastoma and initiation of therapy would likely improve quality of life and may affect outcome (if therapy is started prior to end organ damage).

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

Therapies Under Investigation

Several early-phase clinical trials of small-molecule inhibitors targeting the ALK tyrosine kinase receptor have been completed in individuals with *ALK*-aberrant neuroblastomas. In addition, several trials are ongoing. The role of these agents for the treatment of *ALK*-aberrant neuroblastomas is yet to be elucidated.

- NCT03107988. Phase I study of lorlatinib (an ALK tyrosine kinase inhibitor) as a single agent or in combination with chemotherapy for individuals with relapsed/recurrent neuroblastoma (NANT2015-02)
- NCT05489887. Phase II trial of naxitamab added to induction therapy for individuals with newly diagnosed high-risk neuroblastoma, in which ceritinib will be added to treatment regimens for individuals with an *ALK* pathogenic variant or amplification
- NCT03126916. Phase III trial for children with high-risk neuroblastoma, incorporating lorlatinib into the frontline treatment for individuals whose tumors contain an *ALK* aberration

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

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

ALK-related neuroblastic tumor susceptibility is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *ALK*-related neuroblastic susceptibility inherited an *ALK* pathogenic variant from a heterozygous parent.
  - Because of reduced penetrance, a parent may have a germline *ALK* activating pathogenic variant without having developed a neuroblastic tumor (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma) [Janoueix-Lerosey et al 2008, Mossé et al 2008].
  - As yet, no tumor types other than neuroblastoma, ganglioneuroma, or ganglioneuroblastoma have been reported to be associated with germline *ALK* activating pathogenic variants, and no data regarding the cancer risk for heterozygous adult parents of a child with *ALK*-related neuroblastic susceptibility have been published.
- Some individuals diagnosed with *ALK*-related neuroblastic tumor susceptibility have the disorder as the result of a *de novo* germline *ALK* activating pathogenic variant. *De novo* germline pathogenic variants have been reported; the proportion of probands who have a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* germline *ALK* activating pathogenic variant to evaluate their genetic status and inform recurrence risk assessment.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with *ALK*-related neuroblastic tumor susceptibility may appear to be negative because of reduced penetrance or failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the germline *ALK* pathogenic variant identified in the proband.

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 of the proband is affected or has a germline *ALK* activating pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. The likelihood that a sib who inherits the *ALK* pathogenic variant will develop a neuroblastic tumor is not yet definitively known, but penetrance is estimated to be around 50%.
- If the proband has a known *ALK* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- The sibs of a proband with clinically unaffected parents whose *ALK* variant status is unknown are still at increased risk (for the disorder) because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with *ALK*-related neuroblastic tumor susceptibility has a 50% chance of inheriting the *ALK* pathogenic variant.
- The likelihood that a child who inherits the *ALK* pathogenic variant will develop a neuroblastic tumor is unknown, though the penetrance is estimated to be around 50% (significantly higher than in a child in the general population, in which neuroblastomas are rare).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a germline *ALK* activating pathogenic variant, members of the parent's family may be at risk for neuroblastomas or related tumors.

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.

Testing of at-risk asymptomatic relatives of individuals with *ALK*-related neuroblastic tumor susceptibility is possible after molecular genetic testing has identified the specific germline *ALK* pathogenic variant in the family. Although molecular genetic testing can identify the presence of a germline *ALK* pathogenic variant and thereby identify family members at high risk for neuroblastomas, it cannot predict whether neuroblastomas, ganglioneuromas, or ganglioneuroblastomas will develop.

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 affected, have a germline *ALK* activating pathogenic variant, or are at risk of having a germline *ALK* activating pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the germline *ALK* activating pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Note: Although molecular genetic testing can identify the presence of a germline *ALK* activating pathogenic variant, it cannot predict whether neuroblastomas will develop.

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.

- **Children's Neuroblastoma Cancer Foundation**
  Phone: 630-380-4058
  Email: info@cncfhope.org
  www.cncfhope.org
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **American Childhood Cancer Organization**
  Phone: 855-858-2226
  www.acco.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org

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. ALK-Related Neuroblastic Tumor Susceptibility: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALK	2p23.2-p23.1	ALK tyrosine kinase receptor	ALK database	ALK	ALK

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 ALK-Related Neuroblastic Tumor Susceptibility (View All in OMIM)

105590	ANAPLASTIC LYMPHOMA KINASE; ALK
613014	NEUROBLASTOMA, SUSCEPTIBILITY TO, 3; NBLST3

Molecular Pathogenesis

ALK encodes a single chain receptor tyrosine kinase, the ALK tyrosine kinase receptor; its normal function is not known [Mossé et al 2008]. Expression is restricted to the developing central and peripheral nervous system, with a postulated role in regulation of neuronal differentiation.

ALK is predicted to function as an oncogene in the pathogenesis of neuroblastomas [Chen et al 2008, George et al 2008, Janoueix-Lerosey et al 2008, Mossé et al 2008]. In *ALK*-related neuroblastomas, both germline and somatic pathogenic variants are found exclusively within the *ALK* tyrosine kinase domain. Pathogenic variants in the *ALK* tyrosine kinase domain result in constitutive phosphorylation and activation of the ALK tyrosine kinase receptor [Mossé et al 2008], and are predicted with high probability to drive oncogenesis [Mossé et al 2008]. Both *ALK* pathogenic variants and amplification have been shown to have direct oncogenic effects, as evidenced by autophosphorylation of mutated strains and activation of downstream targets in neuroblastoma cell lines containing *ALK* pathogenic variants and amplification [Janoueix-Lerosey et al 2008, Mossé et al 2008]. Tumors with aberrant *ALK* signaling display transforming potential in vivo, inducing soft agar colony formation in mutated cell lines, rapid tumor growth in nude mice, and increased apoptosis in response to small-interfering RNA or small-hairpin RNA targeted against *ALK* [Chen et al 2008, George et al 2008, Park et al 2008].

Mechanism of disease causation. Gain of function

Table 6. *ALK* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004304.5 NP_004295.2	c.3383G>C	p.Gly1128Ala	See Genotype-Phenotype Correlations & Molecular Genetics, Cancer and Benign Tumors.
	c.3497T>G	p.Met1166Arg	See Molecular Genetics, Cancer and Benign Tumors.
	c.3509T>A	p.Ile1170Asn	
	c.3509T>G	p.Ile1170Ser	
	c.3512T>A	p.Ile1171Asn	
	c.3522C>A	p.Phe1174Leu	
	c.3520T>G	p.Phe1174Val	See Genetically Related Disorders & Molecular Genetics, Cancer and Benign Tumors.
	c.3575G>C	p.Arg1192Pro	See Molecular Genetics, Cancer and Benign Tumors.
	c.3586C>A	p.Leu1196Met	
	c.3734T>G	p.Phe1245Cys	
	c.3733T>G	p.Phe1245Val	See Genetically Related Disorders & Molecular Genetics, Cancer and Benign Tumors.
	c.3824G>A	p.Arg1275Gln	Most common germline & somatic pathogenic variant; accounts for ~45% of germline pathogenic variants [Wood et al 2009].
	c.3833A>C	p.Tyr1278Ser	See Molecular Genetics, Cancer and Benign Tumors.

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.

Cancer and Benign Tumors

Somatic *ALK* pathogenic variants. The frequency of somatic *ALK* pathogenic variants involving neuroblastoma tumor tissue is 8%-10% and enriched in high-risk neuroblastomas, where aberrations are identified in 14% of neoblastic tumors [Pugh et al 2013, Bresler et al 2014]. Disruption of normal *ALK* signaling likely plays a critical role in neuroblastic tumor pathogenesis. Furthermore, it appears that individuals whose tumor contains a somatic *ALK* activating pathogenic variant have a poorer prognosis than individuals with otherwise similar tumor stage and biology [Chen et al 2008, Mossé et al 2008, Mossé et al 2013, Pugh et al 2013, Bresler et al 2014].

Preclinical data suggest that responsiveness to crizotinib may depend on the presence or absence and specific type of somatic *ALK* pathogenic variant (i.e., in the tumor). Specifically, tumors with the somatic *ALK* pathogenic variants p.Phe1174Leu, p.Gly1128Ala, p.Met1166Arg, p.Phe1245Cys, p.Phe1245Val, and p.Tyr1278Ser are relatively crizotinib resistant, whereas the p.Ile1170Asn, p.Ile1170Ser, p.Ile1171Asn, p.Leu1196Met, and p.Arg1275Gln variants are sensitive to crizotinib. The p.Arg1192Pro variant is intermediate in sensitivity [Mossé et al 2013]. Subsequent Phase II and III clinical trials for neuroblastomas will incorporate *ALK* molecular genetic testing for the tumors of all individuals enrolled in the trial.

Several recent clinical trials have incorporated ALK tyrosine kinase inhibitors into therapy. These trials are not specific to individuals with *ALK* germline pathogenic variants but have included small numbers of individuals with neuroblastoma and an *ALK* germline pathogenic variant with good response. One (of one) individual with a germline *ALK* pathogenic variant responded to lorlatinib, and 2/2 and 3/3 individuals with a germline *ALK* pathogenic variant responded to crizotinib in separate studies [Mossé et al 2013, Fischer et al 2021, Goldsmith et al 2023].

These data have been confirmed in other studies as well. For example, human neuroblastoma-derived cell lines containing mutated proteins with the p.Arg1275Gln substitution, the most common abnormal protein described in *ALK*-related neuroblastoma [Azarova et al 2011], were more sensitive to the small-molecule *ALK* inhibitor PF-02341066 than cell lines containing proteins with the p.Phe1174Leu substitution or those without *ALK* aberrations [Wood et al 2009]. The cell line most sensitive to pharmacologic inhibition contains high-level amplification of *ALK* (wild type sequence). Clinical correlation in individuals with neuroblastoma has yet to be determined [Wood et al 2009].

The variant p.Phe1174Leu, associated with amplification of the oncogene *MYCN*, is found as a somatic pathogenic variant in 30% of sporadic neuroblastoma tumors that contain an *ALK* pathogenic variant [Carpenter & Mossé 2012]. Individuals with this pathogenic variant have a poorer prognosis than individuals with *MYCN* amplification alone [Azarova et al 2011].

Somatic amplification of *ALK* on chromosome 2p23 has also been identified in a subset of sporadic neuroblastomas with unfavorable biologic characteristics and aggressive clinical course. Individuals whose tumor contains an *ALK* amplification (i.e., >10 copies of *ALK*) have a poorer prognosis than individuals with otherwise similar tumor stage and biology.

Somatic translocations involving *ALK* resulting in fusion proteins have been identified in anaplastic large-cell lymphomas, non-small-cell lung cancer, inflammatory myofibroblastic tumors, diffuse large B-cell lymphomas, and squamous cell carcinomas of the esophagus. In all these tumors, aberrant ALK tyrosine kinase receptor signaling occurs as a result of a chromosome translocation involving the *ALK* locus at 2p23.

Chapter Notes

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