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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 neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Neuroblastoma is a more malignant tumor and ganglioneuroma a more benign tumor. Depending on the histologic findings, ganglioneuroblastoma can behave in a more aggressive fashion, like neuroblastoma, or in a benign fashion, like ganglioneuroma. Preliminary data from the ten reported families with *ALK*-related neuroblastic tumor susceptibility suggest an overall penetrance of approximately 57% 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.

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 neuroblastoma and ganglioneuroblastoma 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:

- **Asymptomatic children.** Physical examination, abdominal ultrasound examination, chest x-ray, and measurement of urine catecholamine metabolite levels (homovanillic acid and vanillylmandelic acid) every three months between birth and age six years. Physical examination, abdominal ultrasound

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examination, chest x-ray, and measurement of urine catecholamine metabolite levels (homovanillic acid and vanillylmandelic acid) every six months between age six years and ten years. Screening beyond age ten years is not indicated.

- **After successful treatment of a neuroblastic tumor**. Screening for neuroblastoma should continue since children with *ALK*-related neuroblastoma are at risk of developing multiple primary tumors. Screening should continue as described above until age ten years.

Evaluation of relatives at risk: It is appropriate to test relatives at risk (i.e., 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 neuroblastoma 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, with reduced penetrance. Some individuals diagnosed with *ALK*-related neuroblastic susceptibility have an affected parent who may have had any one of the three neuroblastic tumor types. *De novo* germline pathogenic variants have been reported; the proportion of individuals with 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; however, the likelihood that a child who inherits the *ALK* pathogenic variant will develop a neuroblastic tumor is unknown. Prenatal testing is possible for pregnancies at increased risk in families in which the pathogenic variant has been identified.

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 individuals 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.

Written guidelines for selection of individuals with a neuroblastic tumor to be tested for germline *ALK* pathogenic variants are under development, and no consensus opinion currently exists.

Considerations for testing for germline *ALK* pathogenic variants include the following strong and moderate recommendations [Bourdeaut et al 2012, Brodeur et al 2017].

Recommendations Regarding 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

ALK-related neuroblastic tumor susceptibility **is established** in a proband 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 (see Table 1).

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) 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. 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 Probands with a Pathogenic Variant [2] Detectable 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 allelic 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 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.
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, p.Ile1250Thr, 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 neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Within this spectrum, neuroblastoma represents a more malignant tumor and ganglioneuroma a more benign tumor. The three neuroblastic tumor types are defined histologically. Depending on the histologic findings, ganglioneuroblastoma can behave in a benign fashion, like ganglioneuroma, or in a more aggressive fashion, like neuroblastoma.

Data from the ten reported families with *ALK*-related neuroblastic tumor susceptibility suggest that the overall penetrance of this cancer predisposition syndrome is around 57% [Eng 2008]. A recent 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].

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 9 months) than those without familial predisposition (age 2-3 years) [Park et al 2008].

Multiple primary tumors. Individuals with familial neuroblastoma 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].

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 neuroblastoma 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 neuroblastoma 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 (neuroblastoma 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 neuroblastoma or outcome of neuroblastoma have been established [Azarova et al 2011].

- 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%).
- 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 harbor 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 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. Disorders to Consider in the Differential Diagnosis of *ALK*-Related Neuroblastic Tumor Susceptibility (*ALK*-NTS)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*ALK*-NTS	Distinguishing from *ALK*-NTS
PHOX2B-related familial neuroblastoma susceptibility (OMIM 613013)	*PHOX2B*	AD	Familial neuroblastoma	• Hirschsprung disease • ↓ esophageal motility • Congenital central hypoventilation syndrome • Dysmorphic facial features (downslanting palpebral fissures, small nose, triangular mouth, low-set, posteriorly rotated ears)
ROHHAD syndrome [1]	Unknown		Ganglioneuroblastoma, ganglioneuroma	• Rapid-onset obesity • Hypothalamic dysfunction • Hypoventilation • Autonomic dysregulation
KIF1B-neuroblastoma susceptibility (OMIM 256700)	*KIF1B*	AD	Neuroblastoma, ganglioneuroma	Pheochromocytomas, leiomyosarcoma
Neurofibromatosis 1	*NF1*	AD	Neuroblastoma	• Café au lait macules, intertriginous freckling, cutaneous neurofibromas • Peripheral nerve sheath tumors • Iris Lisch nodules • Learning disabilities
Costello syndrome	*HRAS*	AD	Neuroblastoma	• Characteristic facies • Growth deficiency • Developmental delay • Characteristic hair & skin findings • Cardiac disease
Noonan syndrome	≥8 genes	AD	Neuroblastoma	• Characteristic facies • Short stature • Congenital heart disease • Developmental delay • Leukemias, rhabdomyosarcoma
Li-Fraumeni syndrome	*TP53*	AD	Neuroblastoma	Soft-tissue sarcomas, osteosarcoma, breast cancer, brain tumors, adrenocortical carcinoma, leukemias

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*ALK*-NTS	Distinguishing from *ALK*-NTS
Beckwith-Weidemann syndrome	*CDKN1C* [2]	Simplex or AD	Neuroblastoma	• Macrosomia, macroglossia, visceromegaly, omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, renal abnormalities, hemihyperplasia • Wilms tumor, hepatoblastoma, rhabdomyosarcoma

AD = autosomal dominant; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked

1. Ize-Ludlow et al [2007]

2. Beckwith-Wiedemann syndrome is associated with abnormal regulation of gene transcription in the imprinted domain on chromosome 11p15.5, which can be caused by different genetic mechanisms: abnormal methylation of one of two differently methylated regions (DMRs), paternal uniparental disomy, or pathogenic variants in *CDKN1C*.

Management

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 this section are recommended:

- Physical examination to assess for clinical manifestations of neuroblastic tumors such as an abdominal mass, Horner syndrome, and/or cutaneous lesions
- Radiograph of the chest and ultrasound examination of the abdomen, the most common sites for neuroblastic tumor development
- Measurement of urine catecholamines, as homovanillic acid and vanillylmandelic acid may be elevated in the presence of a neuroblastic tumor
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Children who develop neuroblastic tumors (neuroblastomas, ganglioneuroblastoma, or ganglioneuroma) should be evaluated and treated by a pediatric oncologist at a pediatric cancer center.

Neuroblastoma and ganglioneuroblastoma. 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. Clinical trials are ongoing to study the efficacy of *ALK*-targeted therapy in the setting of relapsed and refractory neuroblastoma and ganglioneuroblastoma (see Therapies Under Investigation).

The management guidelines for neuroblastoma or ganglioneuroblastoma are complex [Irwin & Park 2015]:

- Depending on the age of the affected individual, stage of the tumor, and biologic characteristics of the tumor, treatment may involve observation or surgical resection.
- Tumors with risk for metastatic spread or those that have already metastasized require chemotherapy and sometimes radiation therapy, stem cell transplantation, and immunotherapy.

Ganglioneuromas are typically removed by surgical resection and require no further therapy.

Surveillance

Asymptomatic children at risk. Guidelines for the screening of individuals with familial neuroblastoma – including those with germline *ALK* activating pathogenic variants – were published in 2017 [Brodeur et al 2017]. These surveillance recommendations include physical examination, abdominal ultrasound examination, chest x-ray, and measurement of urine catecholamine metabolite levels (homovanillic acid and vanillylmandelic acid) at the following frequency:

- **Birth to age 6 years.** Every three months
- **Age 6-10 years.** Every six months

Screening beyond age ten years is not indicated.

After successful treatment of a neuroblastic tumor, screening for neuroblastic tumors should continue since children with *ALK*-related neuroblastic tumor susceptibility are at risk of developing multiple primary tumors. Screening should continue as described above until ten years of age.

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).

Note: Sibs of all probands with neuroblastoma have an increased chance of developing neuroblastoma themselves, with a standardized incidence ratio of 9.7 compared to the general population [Mossé et al 2008]. This increased risk is likely due in part to the possibility of inherited germline *ALK* pathogenic variants in some children with neuroblastoma.

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 domain have been completed in individuals with *ALK*-aberrant neuroblastoma. In addition, several trials are ongoing. The role of these agents for the treatment of *ALK*-aberrant neuroblastoma is yet to be elucidated. Currently, the Children's Oncology Group Phase III trial for children with high-risk neuroblastoma is incorporating the ALK inhibitor crizotinib into the frontline treatment for individuals whose tumors harbor 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 may have the disorder as the result of a *de novo* germline *ALK* activating pathogenic variant. *De novo* germline pathogenic variants have been reported; their proportion is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* germline *ALK* activating pathogenic variant.
- If the germline *ALK* activating pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.
- 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 confirmed that neither of the parents has 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 likely a 45%-50% chance.
- 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 theoretic 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 theoretic 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 high (57%) [Eng 2008] and the relative risk (compared to a child in the general population) of developing a neuroblastic tumor is substantial.

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 neuroblastoma 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.

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 identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 an *ALK* pathogenic variant, it cannot predict whether neuroblastoma, ganglioneuroma, or ganglioneuroblastoma 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the germline *ALK* activating pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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 neuroblastoma 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
  www.cancer.org
- **American Childhood Cancer Organization**
  Phone: 855-858-2226
  www.acco.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  www.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 is predicted to function as an oncogene in the pathogenesis of neuroblastoma [Chen et al 2008, George et al 2008, Janoueix-Lerosey et al 2008, Mossé et al 2008]. Somatic chromosomal translocations causing constitutive activation of *ALK* are known to mediate malignant transformation in other types of tumors such as non-small-cell lung cancer (*ALK/EML4* fusion protein) and anaplastic large-cell lymphoma (*ALK/NPM1*) [Palmer et al 2009].

In *ALK*-related neuroblastoma, both germline and somatic pathogenic variants are found exclusively within the tyrosine kinase domain of *ALK*. These pathogenic variants lead to constitutive phosphorylation and activation of the ALK protein. 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.

Gene structure. *ALK* comprises 29 coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The vast majority (91%) of *ALK* pathogenic variants fall within the kinase domain [Chen et al 2008]. Missense variants in the tyrosine kinase domain of *ALK* are associated with *ALK*-related neuroblastic tumor susceptibility [Mossé et al 2008].

The variant p.Arg1275Gln, the most commonly reported germline pathogenic variant, is found in approximately 45% of individuals with a germline pathogenic variant [Wood et al 2009]; it is also the most common somatic pathogenic variant.

Table 3. *ALK* Germline Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.3383G>C	p.Gly1128Ala	NM_004304.3 NP_004295.2
c.3452C>T	p.Thr1151Met [1]	
c.3749T>C	p.Ile1250Thr [2]	
c.3520T>G	p.Phe1174Val [3, 5]	
c.3733T>G	p.Phe1245Val [3]	
c.3824G>A	p.Arg1275Gln [4, 5]	

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. George et al [2008]
2. Mossé et al [2008]
3. de Pontual et al [2011]
4. Most common allele
5. See Genotype-Phenotype Correlations.

Normal gene product. *ALK* encodes a 1,620-amino acid protein that is a single chain receptor tyrosine kinase; 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.

Abnormal gene product. Pathogenic variants in the tyrosine kinase domain of *ALK* result in constitutive phosphorylation [Mossé et al 2008] and are predicted with high probability to drive oncogenesis [Mossé et al 2008]. Both *ALK* pathogenic variants and amplifications have been shown to have direct oncogenic effect, as evidenced by autophosphorylation of mutated strains and activation of downstream targets in neuroblastoma cell lines harboring *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 or small-hairpin RNA targeted against *ALK* [Chen et al 2008, George et al 2008, Park et al 2008].

Cancer and Benign Tumors

Fusion proteins resulting from somatic translocations involving *ALK* have been implicated in several types of cancer. In all these tumors, aberrant ALK signaling occurs as a result of a chromosome translocation involving the *ALK* locus at 2p23. In contrast, germline and somatic *ALK* pathogenic variants have only been discovered in neuroblastoma.

Fusion proteins

- Anaplastic large-cell lymphomas harbor a characteristic chromosome 2;5 translocation involving *ALK* and *NPM1* (encoding nucleophosmin), which may be referred to as *ALK/NPM1* [Morris et al 1994].

- *ALK/EML4* fusion transcripts are found in a subset of individuals with non-small-cell lung cancer, all of whom lack *EGFR* pathogenic variants [Soda et al 2007].
- *ALK* fusion proteins have also been described in inflammatory myofibroblastic tumors, diffuse large B-cell lymphomas, and squamous cell carcinomas of the esophagus [Palmer et al 2009].

Somatic *ALK* pathogenic variants. The frequency of somatic *ALK* pathogenic variants involving neuroblastoma tumor tissue is 6%-12% [Santani A & Maris J, personal communication]. Disruption of normal *ALK* signaling is likely to play a critical role in neuroblastic tumor pathogenesis. Furthermore, it appears that individuals whose tumor harbors a somatic *ALK* activating pathogenic variant or *ALK* amplification (i.e., >10 copies of *ALK*) 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; Santani A & Maris J, personal communication].

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 neuroblastoma will incorporate *ALK* molecular genetic testing for the tumors of all individuals enrolled in the trial.

These data have been confirmed in other studies as well. For example, human neuroblastoma-derived cell lines harboring 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 harboring proteins with the p.Phe1174Leu substitution or those without *ALK* aberrations [Wood et al 2009]. The cell line most sensitive to pharmacologic inhibition harbors 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 harbor an *ALK* pathogenic variant [Carpenter & Mossé 2012]. Individuals with this pathogenic variant have a worse prognosis than individuals with *MYCN* amplification alone [Azarova et al 2011].

Chapter Notes

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- 17 January 2019 (sw) Comprehensive update posted live
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References

Published Guidelines / Consensus Statements

American Society of Clinical Oncology. Policy statement update: genetic testing for cancer susceptibility. Available online. 2010. Accessed 5-24-22.

Literature Cited

Azarova AM, Gautam G, George RE. Emerging importance of ALK in neuroblastoma. Semin Cancer Biol. 2011;21:267–75. PubMed PMID: 21945349.

Bourdeaut F, Ferrand S, Brugières L, Hilbert M, Ribeiro A, Lacroix L, Bénard J, Combaret V, Michon J, Valteau-Couanet D, Isidor B, Rialland X, Poirée M, Defachelles AS, Peuchmaur M, Schleiermacher G, Pierron G, Gauthier-Villars M, Janoueix-Lerosey I, Delattre O, et al. ALK germline mutations in patients with neuroblastoma: a rare and weakly penetrant syndrome. Eur J Hum Genet. 2012;20:291–7. PubMed PMID: 22071890.

Brodeur GM, Nichols KE, Plon SE, Schiffman JD, Malkin D. Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr. Clin Cancer Res. 2017;23:e1–e5. PubMed PMID: 28572261.

Carén H, Abel F, Kogner P, Martinsson T. High incidence of DNA mutations and gene amplifications of the ALK gene in advanced sporadic neuroblastoma tumours. Biochem J. 2008;416:153–9. PubMed PMID: 18990089.

Carpenter EL, Mossé YP. Targeting ALK in neuroblastoma--preclinical and clinical advancements. Nat Rev Clin Oncol. 2012;9:391–9. PubMed PMID: 22585002.

Chen Y, Takita J, Choi YL, Kato M, Ohira M, Sanada M, Wang L, Soda M, Kikuchi A, Igarashi T, Nakagawara A, Hayashi Y, Mano H, Ogawa S. Oncogenic mutations of ALK kinase in neuroblastoma. Nature. 2008;455:971–4. PubMed PMID: 18923524.

de Pontual L, Kettaneh D, Gordon CT, Oufadem M, Boddaert N, Lees M, Balu L, Lachassinne E, Petros A, Mollet J, Wilson LC, Munnich A, Brugière L, Delattre O, Vekemans M, Etchevers H, Lyonnet S, Janoueix-Lerosey I, Amiel J. Germline gain-of-function mutations of ALK disrupt central nervous system development. Hum Mutat. 2011;32:272–6. PubMed PMID: 21972109.

Eng C. Cancer: a ringleader identified. Nature. 2008;455:883–4. PubMed PMID: 18923503.

George RE, Sanda T, Hanna M, Fröhling S, Luther W 2nd, Zhang J, Ahn Y, Zhou W, London WB, McGrady P, Xue L, Zozulya S, Gregor VE, Webb TR, Gray NS, Gilliland DG, Diller L, Greulich H, Morris SW, Meyerson M, Look AT. Activating mutations in ALK provide a therapeutic target in neuroblastoma. Nature. 2008;455:975–8. PubMed PMID: 18923525.

Irwin MS, Park JR. Neuroblastoma: paradigm for precision medicine. Pediatr Clin North Am. 2015;62:225–56. PubMed PMID: 25435121.

Ize-Ludlow D, Gray J, Sperling MA, Berry-Kravis EM, Milunsky JM, Farooqi IS, Rand CM, Weese-Mayer DE. Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics. 2007;120:e179–88. PubMed PMID: 17606542.

Janoueix-Lerosey I, Lequin D, Brugières L, Ribeiro A, de Pontual L, Combaret V, Raynal V, Puisieux A, Schleiermacher G, Pierron G, Valteau-Couanet D, Frebourg T, Michon J, Lyonnet S, Amiel J, Delattre O. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. Nature. 2008;455:967–70. PubMed PMID: 18923523.

Liu Z, Thiele CJ. ALK and MYCN: when two oncogenes are better than one. Cancer Cell. 2012;21:325–6. PubMed PMID: 22439928.

Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, Look AT. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994;263:1281–4. PubMed PMID: 8122112.

Mossé YP, Laudenslager M, Longo L, Cole KA, Wood A, Attiyeh EF, Laquaglia MJ, Sennett R, Lynch JE, Perri P, Laureys G, Speleman F, Kim C, Hou C, Hakonarson H, Torkamani A, Schork NJ, Brodeur GM, Tonini GP, Rappaport E, Devoto M, Maris JM. Identification of ALK as a major familial neuroblastoma predisposition gene. Nature. 2008;455:930–5. PubMed PMID: 18724359.

Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, Rolland D, Balis FM, Maris JM, Weigel BJ, Ingle AM, Ahern C, Adamson PC, Blaney SM. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol. 2013;14:472–80. PubMed PMID: 23598171.

Palmer RH, Vernersson E, Grabbe C, Hallberg B. Anaplastic lymphoma kinase: signalling in development and disease. Biochem J. 2009;420:345–61. PubMed PMID: 19459784.

Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. Pediatr Clin North Am. 2008;55:97–120. PubMed PMID: 18242317.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Ritenour LE, Randall M, Bosse K, Diskin S. Genetic susceptibility to neuroblastoma: current knowledge and future directions. Cell Tissue Res. 2018;372:287–307. PubMed PMID: 29589100.

Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561–6. PubMed PMID: 17625570.

Weiss T, Taschner-Mandl S, Bileck A, Slany A, Kromp F, Rifatbegovic F, Frech C, Windhager R, Kitzinger H, Tzou CH, Ambros PF, Gerner C, Ambros IM. Proteomics and transcriptomics of peripheral nerve tissue and cells unravel new aspects of the human Schwann cell repair phenotype. Glia. 2016;64:2133–53. PubMed PMID: 27545331.

Wood AC, Laudenslager EA, Haglund EA, Attiyeh EF, Pawel B, Courtright J, Plegaria J, Christensen JG, Maris JM, Mosse YP. Inhibition of ALK mutated neuroblastomas by the selective inhibitor PF-02341066. Abstract 10008b. Orlando, FL: American Society of Clinical Oncology Annual Meeting; 2009.

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