ELANE-Related Neutropenia

Includes: Cyclic Neutropenia, Severe Congenital Neutropenia

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Summary

Disease characteristics. *ELANE*-related neutropenia includes congenital neutropenia and cyclic neutropenia, both of which are primary hematologic disorders characterized by recurrent fever, skin and oropharyngeal inflammation (i.e., mouth ulcers, gingivitis, sinusitis, and pharyngitis), and cervical adenopathy. Infectious complications are generally more severe in congenital neutropenia than in cyclic neutropenia.

In congenital neutropenia, omphalitis immediately after birth may be the first sign; in untreated children diarrhea, pneumonia, and deep abscesses in the liver, lungs, and subcutaneous tissues are common in the first year of life. After 15 years with granulocyte colony stimulating factor treatment, the risk of developing myelodysplasia (MDS) or acute myelogenous leukemia AML is approximately 15%-25%.

Cyclic neutropenia is usually diagnosed within the first year of life based on approximately three-week intervals of fever and oral ulcerations and regular oscillations of blood cell counts. Cellulitis, especially perianal cellulitis, is common during neutropenic periods. Between neutropenic periods, affected individuals are generally healthy. Symptoms improve in adulthood. Cyclic neutropenia is not associated with risk of malignancy or conversion to leukemia.

Diagnosis/testing. The diagnosis of *ELANE*-related neutropenia relies primarily on serial measurements of the absolute neutrophil count (ANC) and clinical findings. Molecular genetic testing of *ELANE*, the only gene in which mutation is known to cause *ELANE*-related neutropenia, is available on a clinical basis. For individuals with well-documented cyclic neutropenia and known affected family members, the mutation detection rate is as high as 100%. For individuals with congenital neutropenia, the mutation detection rate is as high as 80%.

Management. *Treatment of manifestations:* All fevers and infections require prompt evaluation and treatment. Abdominal pain requires evaluation for the potentially lethal complications of peritonitis and bacteremia.

Prevention of primary manifestations: Treatment with granulocyte colony-stimulating factor (G-CSF) ameliorates symptoms and reduces infections in almost all affected individuals. For affected individuals with a well-matched donor, hematopoietic stem cell transplantation (HSCT) may be the preferred treatment option. HSCT is the only alternative therapy for individuals with congenital neutropenia who are refractory to high-dose G-CSF or who undergo malignant transformation.

Prevention of secondary complications: Good dental hygiene.

Surveillance: Those with congenital neutropenia not undergoing HSCT require surveillance for malignant transformation to MDS/AML.

Testing of relatives at risk: Testing of at-risk relatives can help identify those with mild or moderately severe disease who may benefit from treatment. If the family-specific *ELANE* mutation is known, molecular genetic testing can be used; otherwise serial absolute neutrophil counts (ANCs) can be evaluated.

Genetic counseling. *ELANE*-related neutropenia is inherited in an autosomal dominant manner. One parent of a proband is usually affected. *De novo* mutations have been identified; their frequency is unknown. Each child of an individual with an *ELANE* mutation has a 50% chance of inheriting the mutation. Prenatal testing is possible for pregnancies at increased risk if the family-specific mutation is known; however, requests for prenatal testing for conditions such as *ELANE*-related neutropenia which do not affect intellect and have some treatment available are not common.

Diagnosis

Clinical Diagnosis

ELANE-related neutropenia includes congenital neutropenia and cyclic neutropenia. Congenital neutropenia and cyclic neutropenia were initially thought to be distinct disorders; however, following discovery of the molecular basis of *ELANE*-related neutropenia, individuals with findings intermediate between these two phenotypes are also recognized. Nonetheless, identification of the phenotype is helpful for diagnosis, prognosis, and management.

Diagnosis of congenital neutropenia or cyclic neutropenia is based on serial absolute neutrophil counts (ANCs) and clinical findings, including the following:

- **Congenital neutropenia.** Recurrent fevers, sinusitis, gingivitis, and chronic and severe infections in the lung, liver, and soft tissues occurring at irregular intervals
- **Cyclic neutropenia.** Typically, mouth ulcers, pharyngitis, and fever recurring regularly at three-week intervals; inflammation and infection of the sinuses, upper- and lower-respiratory tract, and skin including the perianal area; abdominal pain and signs of an acute abdomen, suggesting sepsis and bacteremia from colonic ulcers

Note: Cyclic neutropenia is distinguished from congenital neutropenia by the regular oscillations of blood neutrophil counts in cyclic neutropenia.

Testing

Congenital neutropenia

- **Absolute neutrophil count (ANC).** Diagnosis requires at least three ANCs lower than 500/µL obtained at least three months after birth.

  Note: (1) The ANC is the white blood cell count (WBC) x % neutrophils. (2) In *ELANE*-related congenital neutropenia, ANCs are usually below 0.2 x 10^9/L. (3) In one series, the mean was 0.112 x 10^9/L.
- **Oscillations.** In some individuals, periods with regular oscillations in blood neutrophil counts can be interspersed with periods in which no oscillations in blood neutrophil counts are apparent.

  Note: Often, serial blood cell counts are needed to assure that individuals suspected of having congenital neutropenia do not have cyclic neutropenia; however, this approach has limitations because, in some cases of cyclic neutropenia, the amplitude of the oscillations may be very low.

- **Other hematopoietic cells**
  - Monocyte counts tend to be increased (i.e., >1.0 x 10^9/L).
  - Platelet counts tend to be increased.
  - Hematocrit tends to be mildly decreased.
- **Bone marrow aspirate** typically shows "maturation arrest" at the promyelocyte or myelocyte stage of neutrophil formation. Increased bone marrow monocytes and eosinophils may be present.
- **Cytogenetic analysis** of bone marrow is normal.

Cyclic neutropenia

- **Absolute neutrophil count (ANC).** Diagnosis requires serial measurements of the ANC daily or at least three times per week for four to six weeks [Dale 2001].
- **Oscillations.** Most affected individuals have an ANC lower than 0.2 x 10^9/L for three to five days at approximately three-week intervals.

  Note: (1) In *ELANE*-related cyclic neutropenia, peak neutrophil counts are usually lower than 0.2 x 10^9/L. (2) Variations in this classic pattern include cycles longer or shorter than three weeks (probably <5% of individuals) and reduced amplitude of oscillations. (3) Relatives of individuals with typical cycles may have neutropenia but lack obvious cycles. (4) Counts in children tend to oscillate more obviously than in adults.
- **Other hematopoietic cells**
  - Oscillations of other cells, including lymphocytes, eosinophils, and platelets may be observed.
  - Usually, a reciprocal increase in blood monocytes and reticulocytes occurs during the neutrophil nadir.
- **Bone marrow aspirate** shows an abnormality similar to that in congenital neutropenia when neutrophil counts are the lowest; at other times, maturation of cells of the neutrophil lineage is near normal.

Molecular Genetic Testing

Gene. *ELANE* (previously known as *ELA2)* is the only gene in which mutation is known to cause *ELANE*-related neutropenia.

Clinical testing

- **Sequence analysis**

  Cyclic neutropenia. Mutations in *ELANE* were initially reported in 100% of individuals with well-documented cyclic neutropenia [Horwitz et al 1999, Dale et al 2000]. Subsequently, *ELANE* mutations were found in 94 of 105 (90%) of a more diverse population with a clinical diagnosis of cyclic neutropenia; i.e., diagnosis based on clinical history and a limited number of serial neutrophil counts [Aprikyan et al 2002]. Further experience indicates that most individuals with a clinical diagnosis of cyclic neutropenia in whom a mutation in *ELANE* is not found are atypical in some way; i.e., oscillations are not consistently at the usual interval of approximately 21 days, the fluctuations are not from near zero at the nadir to less than approximately 2.0 x 10^9/L at the peak, or serial neutrophil count data are insufficient to be certain about oscillations and fluctuations.

  Congenital neutropenia. Mutations of *ELANE* were initially reported in 88% of individuals with congenital neutropenia [Dale et al 2000]. Further studies showed that 38%-80% of individuals with congenital neutropenia have heterozygous mutations [Aprikyan et al 2002,

Ancliff et al 2003b, Bellanne-Chantelot et al 2004]; this broad range probably depends on the selectivity of the pre-test assessments.

Table 1. Summary of Molecular Genetic Testing Used in *ELANE*-Related Neutropenia

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method and Phenotype [1]		Test Availability
			Cyclic Neutropenia	Congenital Neutropenia	
ELANE	Sequence analysis	Sequence variants [2]	90%-100% [3]	38%-80% [3]	Clinical Testing

Test Availability refers to availability in the GeneTests Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations.

3. Aprikyan et al [2002], Ancliff et al [2003b], Bellanne-Chantelot et al [2004]

Interpretation of test results. Individuals thought to have congenital neutropenia who do not have an *ELANE* mutation may have mutations in other genes associated with abnormalities of immune or autoimmune mechanisms (see Differential Diagnosis).

Mutations in more than one gene associated with neutropenia have been identified in some individuals [Germeshausen et al 2010].

For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm/establish the diagnosis in a proband

- Diagnosis of congenital neutropenia and cyclic neutropenia depends on ANC obtained over specific time intervals.
- Bone marrow examination is often helpful to confirm the diagnosis of congenital neutropenia and cyclic neutropenia and to rule out other disorders such as myelodysplasia or leukemia.

- The finding of an *ELANE* mutation in an individual with neutropenia establishes the diagnosis of *ELANE*-related neutropenia.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *ELANE*.

Clinical Description

Natural History

Congenital neutropenia. Infectious complications are generally more severe in congenital neutropenia than in cyclic neutropenia. In both conditions, individuals have fever and recurrent skin and oropharyngeal inflammation; i.e., mouth ulcers, gingivitis, sinusitis, pharyngitis, and cervical adenopathy. In congenital neutropenia, diarrhea, pneumonia, and deep abscesses in the liver, lung, and subcutaneous tissues are common. Omphalitis immediately after birth may be the first sign [Zeidler & Welte 2002]. Bacteremia occurs infrequently but has severe consequences in affected individuals. Most congenital neutropenia is diagnosed because of fever and severe infection in infants and young children.

Treatment with granulocyte colony-stimulating factor (G-CSF) raises blood neutrophil levels and reduces all of these complications in more than 90% of affected individuals [Zeidler & Welte 2002, Dale et al 2003].

Individuals with congenital neutropenia with or without an *ELANE* mutation who are treated with G-CSF have approximately equal risk for myelodysplasia syndrome (MDS)/acute myelogenous leukemia (AML). The respective cumulative incidences 15 years after starting treatment with G-CSF were 36% and 25% ($P = 0.96$) [Rosenberg et al 2006, Rosenberg et al 2008].

MDS/AML was reported in individuals with severe congenital neutropenia before the availability of G-CSF treatment. Data from a prospective study of 374 persons with severe congenital neutropenia on long-term treatment with G-CSF showed that the overall risk of MDS/AML was 15%-25% at 15 years on treatment. Overall, G-CSF reduced mortality from sepsis, but uncovered an underlying disposition to MDS/AML. Individuals requiring higher doses of G-CSF, i.e., those requiring more than 8 µg/kg/day to achieve a mean neutrophil count equal to the group median (2.188×10^9/L), were at increased risk of death from both sepsis and MDS/AML, compared to those responding to lower doses [Rosenberg et al 2010].

Cyclic neutropenia. Cyclic neutropenia is usually diagnosed soon after birth or within the first year of life based on a pattern of recurrent fever and oral ulcerations with serial blood cell counts showing regular oscillations.

Untreated individuals have recurrent oropharyngeal inflammation; they are particularly prone to developing oral ulcers at approximately three-week intervals. Cellulitis, especially perianal cellulitis, is common during the neutropenic periods. Bacteremia is rare; the greatest risk appears to be for death from necrotizing enterocolitis, peritonitis, and *Clostridium* and/or *E. coli* sepsis [Barnes et al 2004].

Symptoms tend to be more severe in children than in adults. Palmer et al [1996] reported that more than 60% of individuals with cyclic neutropenia experience oral ulcerations, gingivitis, lymphadenopathy, fever, pharyngitis/tonsillitis, fatigue, or skin infections five or more times a year. More than 30% of adults report five or more episodes per year of sinusitis and/or otitis media, and over 20% of children report at least five episodes per year of bone pain or tooth abscesses. More than 10% of individuals report pneumonia, bronchitis, diarrhea, or anal ulcers. Serious neonatal infections and sepsis are rare.

Between neutropenic periods, affected individuals are generally healthy.

Symptoms improve in adulthood. Skin infections, fever, lymphadenopathy, and pharyngitis occur less frequently. Sinusitis, headache, and bone pain remain the most common symptoms. Oral ulcers, fatigue, and gingivitis also occur frequently. Permanent tooth loss resulting from chronic gingivitis, tooth abscesses, and alveolar bone loss in adolescence or young adulthood is common.

There are no associated congenital abnormalities. Cyclic phenomena in other organ systems have not been recognized.

Cyclic neutropenia is not associated with an increased risk of malignancy or conversion to leukemia. However, confusion may arise when the series of counts is insufficient to clearly determine if a patient has congenital or cyclic neutropenia [Dale et al 2000, Dale et al 2003].

Genotype-Phenotype Correlations

Genotype-phenotype correlations are only roughly defined for *ELANE*-related neutropenia. Although the patterns of mutations in *ELANE*-associated cyclic neutropenia and congenital neutropenia are distinct on a population basis, the patterns of mutations do overlap, indicating that the distinction between cyclic neutropenia and congenital neutropenia is primarily based on clinical findings and only secondarily on genotype [Dale et al, unpublished data]. Newburger et al [2010] identified individuals with the same mutation but different clinical phenotypes.

Some *ELANE* mutations now appear to be exclusively or almost exclusively associated with cyclic neutropenia and no recognized risk of evolution to acute myelogenous leukemia (AML), whereas other mutations may possibly be associated with severe congenital neutropenia and increased risk of AML [Bellanne-Chantelot et al 2004].

Analysis of the tertiary structure of neutrophil esterase suggested that mutations at the active site of the enzyme cause cyclic neutropenia, and mutations preventing normal folding and packaging of leukocyte elastase cause severe congenital neutropenia [Dale et al 2000, Kollner et al 2006].

Penetrance

Penetrance in cyclic neutropenia is complete, but severity of manifestations varies among affected family members. Several families with three- and four-generation involvement have been described.

Anticipation

There is no clear evidence for anticipation in congenital or cyclic neutropenia. However, because a founder (i.e., the first known affected individual in a family) may be mosaic for an *ELANE* mutation and thus have a milder phenotype, his/her offspring may have more severe disease, giving the appearance of anticipation [Ancliff et al 2002].

Nomenclature

Originally described as an autosomal recessive disorder, Kostmann syndrome now appears to be genetically heterogeneous. Although the cause of Kostmann syndrome is largely unknown, a subset of individuals previously described as having Kostmann syndrome are now known to have heterozygous mutations in *ELANE* and, therefore, to be part of the spectrum of *ELANE*-related neutropenia [Zeidler & Welte 2002]. Of interest, one individual in the kindred originally described by Kostmann has an *ELANE* mutation [Carlsson et al 2006].

Prevalence

Congenital neutropenia has an estimated frequency of 2:1,000,000-3:1,000,000 in the general population.

Cyclic neutropenia has an estimated frequency of 1:1,000,000 in the general population, including both familial cases and simplex cases (i.e., single occurrences in a family).

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Congenital neutropenia. The differential diagnosis of congenital neutropenia includes the following disorders:

Isolated neutropenia:

- Kostmann syndrome, an autosomal recessive form of severe congenital neutropenia:
    - Klein et al [2007] identified homozygous mutations in *HAX1* (encoding HCLS1-associated protein X-1) in several individuals with Kostmann syndrome.

      Note: *De novo* heterozygous *ELANE* mutations (autosomal dominant severe congenital neutropenia) are much more common than *HAX1* mutations (autosomal recessive congenital neutropenia) as a cause of simplex cases of severe congenital neutropenia (i.e., a single occurrence in a family) [Xia et al 2009]. For this reason, it is usually

best to first sequence *ELANE* in seeking to determine the genetic basis for severe congenital neutropenia.
    - Mutations in *G6PC3* (encoding glucose-6-phosphate 3) result in an autosomal recessive form of severe congenital neutropenia [Klein 2011].
    - A mutation in *GFI1* (encoding zinc finger protein Gfi-1) has been reported in one person with severe congenital neutropenia [Person et al 2003].
- Benign familial neutropenia, an autosomal dominant form of congenital neutropenia with milder neutropenia and less severe symptoms
- Autoimmune neutropenia, usually attributed to anti-neutrophil antibodies
- Idiopathic neutropenia, isolated neutropenia of unknown cause
- Cyclic neutropenia

Syndromes with congenital neutropenia:

- Glycogen storage disease type Ib
- Shwachman-Diamond syndrome
- Reticular dysgenesis
- Cartilage-hair hypoplasia
- Chediak-Higashi syndrome
- Griscelli syndrome
- Barth syndrome
- Wiskott-Aldrich syndrome
- Dyskeratosis congenita
- Myelokathexis (WHIM syndrome)
- Severe congenital neutropenia, autosomal recessive, 4

Note to clinicians: For a patient-specific 'simultaneous consult' related to congenital neutropenia, go to , an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Cyclic neutropenia. Other diagnoses confused with cyclic neutropenia include congenital neutropenia and idiopathic, autoimmune, and benign neutropenia of childhood.

Note to clinicians: For a patient-specific 'simultaneous consult' related to cyclic neutropenia, go to (registration or institutional access required).

Fever. Other disorders with recurrent fevers are familial Mediterranean fever and PFAPA (**p**eriodic **f**ever, **a**denopathy, **p**haryngitis, and **a**phthous ulcers).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *ELANE*-related neutropenia, the following are recommended:

- Dental examination for gingival and periodontal disease

- Evaluation (particularly of those with severe congenital neutropenia) by an otolaryngologist and pulmonologist for chronic sinopulmonary inflammation and deep abscesses
- Evaluation of individuals with severe congenital neutropenia for evidence of myelodysplasia or leukemia

Treatment of Manifestations

Conventional management includes prompt treatment of fevers and infections with antibiotics.

Individuals with abdominal pain require careful evaluation for the potentially lethal complications of peritonitis and bacteremia.

Prevention of Primary Manifestations

Granulocyte colony-stimulating factor (G-CSF). Treatment with granulocyte colony-stimulating factor (G-CSF) is effective in elevating blood neutrophil counts in both congenital neutropenia and cyclic neutropenia. G-CSF treatment ameliorates the symptoms and problems of infections in almost all affected individuals. (Although both G-CSF and GM-CSF have been used to treat *ELANE*-related neutropenia, G-CSF is much more effective and associated with fewer adverse effects than GM-CSF.)

In cyclic neutropenia, G-CSF shortens the periods of neutropenia as well as the length of the neutropenic cycle. Treatment is known to be effective at least as early as age six months to one year. Studies indicate that treatment is effective with no adverse effects on growth, development, or pregnancy outcome with follow-up to age 18 years [Dale et al 2003; Dale, unpublished observations].

Treatment of cyclic neutropenia requires daily or alternate-day injections of G-CSF, normally in a dose of approximately 2 µg/kg/day. Individuals with congenital neutropenia often require higher doses (e.g., 5-10 µg/kg/day).

Common side effects of G-CSF include bone pain and headache, splenomegaly, and osteoporosis. Vasculitis, rashes, arthralgias, and glomerulonephritis have been infrequently reported [Dale et al 2003].

Hematopoietic stem cell transplantation (HSCT)

- For affected individuals with a well-matched donor, HSCT may be the preferred treatment option [Choi & Levine 2010, Oshima et al 2010].
- HSCT is the only alternative therapy for individuals with congenital neutropenia who are refractory to high-dose G-CSF or who undergo malignant transformation.

Prevention of Secondary Complications

Good dental hygiene with regular hygiene visits (several times per year) and careful brushing and flossing are recommended.

Surveillance

For those individuals with congenital neutropenia not undergoing HSCT, surveillance for evidence of malignant transformation to MDS/AML is critical to allow early therapeutic intervention. Observation should include the following:

- General evaluations by parents and medical personnel several times a year
- Blood counts several times a year
- Annual bone marrow cytogenetic studies because of the frequent association of monosomy 7 and malignant transformation

Note: Although sequencing of the receptor for G-CSF (G-CSF-R) from peripheral blood may also provide evidence of evolution to MDS/AML [Ancliff et al 2003a], its clinical utility is not yet clearly established [Freedman & Alter 2002, Cassinat et al 2004, Beekman & Touw 2010].

Testing of Relatives at Risk

Testing of at-risk relatives can help identify those with mild or moderately severe disease who may benefit from treatment. If the family-specific *ELANE* mutation is known, molecular genetic testing can be used; otherwise serial ANCs can be evaluated.

Note: Complete blood counts (CBCs) obtained weekly for a month until an ANC lower than 0.2×10^9/L is documented in more than one sample confirms the diagnosis. A similar series of counts not showing neutropenia rules out this diagnosis.

Treatment of these individuals with G-CSF or any other modality should be based on medical history and the severity of symptoms. It is not yet clear if there are specific risks (i.e., osteoporosis, myelodysplasia, or leukemia) associated with administering G-CSF to such individuals, but conservative management is recommended.

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

Pregnancy Management

Pregnancies in women with severe chronic neutropenia are at substantial risk for miscarriage.

A review of the records of 88 women (183 pregnancies) with congenital, cyclic, idiopathic or autoimmune neutropenia compared outcomes in those on G-CSF therapy during pregnancy with those not on G-CSF therapy during pregnancy [Boxer et al 2010]. In general the health of all the infants was equivalent for the two groups. Other findings included:

- Reduced risk of fetal loss in the women treated during pregnancy.
- Eleven complications (one premature rupture of membranes, two life-threatening infections, two minor infections, and six premature labors) in 55 women (123 pregnancies) not treated with G-CSF during pregnancy.
- No life-threatening infections, no premature labors, five minor infections, and one patient who developed severe thrombocytopenia in 41 women (60 pregnancies) treated with G-CSF during pregnancy.

Therapies Under Investigation

Unrelated cord blood transplantation for neutropenia is being investigated; outcome appears to depend on the closeness of the match [Mino et al 2004, Nakazawa et al 2004, Ferry et al 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions

Registries

Contact information for voluntary patient registries is provided by *GeneReviews* staff.

Severe Chronic Neutropenia International Registry
Phone: 800-726-4463 (toll-free)
Email: stevensl@neutropenia.ca; carlsonm@neutropenia.ca
www.neutropenia.ca/community/scnir

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

ELANE-related neutropenia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with *ELANE*-related neutropenia have an affected parent.
- If neither parent is known to be affected, it is appropriate to evaluate both parents with complete blood counts (CBCs) obtained weekly for a month until an ANC

lower than 0.2 x 10^9/L is documented in more than one sample. Molecular genetic testing of both parents is appropriate if the disease-causing mutation has been identified in the proband.
- Multiple cases have occurred via sperm donation from a single donor [Boxer et al 2006].
- *De novo* mutations have been identified [Horwitz et al 1999, Aprikyan et al 2002]; the frequency is unknown.

Note: The family history may appear to be negative because of failure to diagnose the disorder in a mildly affected parent; for example, if the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to sibs depends on the genetic status of the parents.
- If a parent of the proband is affected or has the disease-causing mutation, the risk to sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low; although no instances have been reported, germline mosaicism remains a possibility.
- It is appropriate to evaluate the sibs of a proband with complete blood counts (CBCs) obtained weekly for a month until an ANC lower than 0.2 x 10^9/L is documented in more than one sample. Molecular genetic testing of sibs is appropriate if the disease-causing mutation has been identified in the proband.

Offspring of a proband. Each child of an individual with an *ELANE* mutation has a 50% chance of inheriting the mutation.

Other family members of a proband

- The risk to other family members depends on the genetic status of the proband's parents.
- If a parent is affected, his or her family members are at-risk.

Related Genetic Counseling Issues

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

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

Family planning

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

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

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions (like *ELANE*-related neutropenia) that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see .

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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. ELANE-Related Neutropenia: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
ELANE	19p13.3	Leukocyte elastase	CCHMC - Human Genetics Mutation Database Resource of Asian Primary Immunodeficiency Diseases (RAPID)	ELANE

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein

name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

Table B. OMIM Entries for ELANE-Related Neutropenia (View All in OMIM)

130130	ELASTASE, NEUTROPHIL-EXPRESSED; ELANE
162800	CYCLIC NEUTROPENIA
202700	NEUTROPENIA, SEVERE CONGENITAL, 1, AUTOSOMAL DOMINANT; SCN1

Molecular Genetic Pathogenesis

Leukocyte elastase, an enzyme synthesized in neutrophil precursors, is one of the first features of development of the neutrophil's primary granules. The enzyme is normally processed in the Golgi apparatus and packaged in the granules as the fully active enzyme. The cell is probably protected from the enzymatic activity of leukocyte elastase (neutrophil elastase) during synthesis by the terminal peptides that are cleaved just before packaging. It is currently presumed that, in congenital neutropenia and cyclic neutropenia, the abnormal enzyme is not inhibited or packaged normally and, therefore, damages the cells of the neutrophil series during their development. A natural experiment has provided compelling evidence that mutation of *ELANE* results in the destruction of neutrophils before they can enter circulation. The father of an individual with congenital neutropenia was found to be mosaic for the mutant *ELANE* allele; half of his somatic cells tested contained the mutant allele, but it was virtually absent in circulating neutrophils [Ancliff et al 2002]. Cellular studies on pathogenesis of cyclic neutropenia have clearly demonstrated that accelerated apoptosis of neutrophil precursors is the proximate cause of the reduced neutrophil production [Aprikyan et al 2001]. The oscillation of blood counts in cyclic neutropenia is attributed to the excessive cell turnover in the early neutrophil compartments, coupled to a system of long-range regulation by feedback from peripheral tissues [Haurie et al 1998]. The accelerated apoptosis may be mediated by altered expression of pro-apoptotic factors, Bcl-2, or cytoplasmic accumulation and induction of the unfolding protein response [Papadaki & Eliopoulos 2003, Carlsson et al 2004, Massullo et al 2005, Kollner et al 2006].

ELANE, which encodes leukocyte elastase (neutrophil elastase), is closely associated with the genes for other serine esterases, protease 3 and cathepsin G, also packaged in the neutrophil granule. Evidence to date indicates that these proximally located genes are normal in cyclic and congenital neutropenia.

Normal allelic variants. The gene comprises five exons.

Pathologic allelic variants. *ELANE* pathologic allelic variants include missense and nonsense mutations, small deletions/insertions in exons, splicing defects, and changes in 5' regulatory region. In one study, 104 of 125 individuals with congenital neutropenia had 18 different mutations and 94 of 105 probands with cyclic neutropenia were heterozygous for seven different mutations [Aprikyan et al 2002]. Other studies have

generally reported a somewhat lower frequency, the variations probably depending on the pre-test identification and selection of cases.

Normal gene product. Leukocyte elastase (neutrophil elastase) is a 240-amino acid protein with broad proteolytic activities. It is synthesized, processed, and packaged in the granules of neutrophils during the differentiation of myeloblasts to promyelocytes [Garwicz et al 2005].

Abnormal gene product. Three-dimensional structural analysis of leukocyte elastase (neutrophil elastase) based on the mutational patterns suggests that these mutations involve the binding site for this enzyme with its substrates.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

Revision History

- 14 July 2011 (me) Comprehensive update posted live
- 7 July 2009 (cd) Revision: gene symbol *ELA2* replaced with *ELANE* - HGNC
- 9 September 2008 (cg) Comprehensive update posted live
- 4 January 2007 (cd) Revision: *HAX1* mutations identified in individuals with autosomal recessive severe congenital neutropenia (Kostmann disease)
- 21 July 2006 (me) Comprehensive update posted to live Web site
- 13 September 2005 (dd) Revision: Genotype-Phenotype Correlations, Surveillance
- 21 May 2004 (me) Comprehensive update posted to live Web site
- 1 October 2003 (cd) Revision: clinical testing availability
- 17 June 2002 (me) Review posted to live Web site
- 21 September 2001 (dd) Original submission