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ELANE-Related Neutropenia

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Summary

Clinical 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 is established in a proband with suggestive clinical findings and the identification of a heterozygous pathogenic variant in *ELANE* through molecular genetic testing.

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. Immediate treatment with granulocyte colony-stimulating factor (G-CSF) and broad-spectrum antibiotics is important, even

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lifesaving, when an affected individual has signs of serious infection, which may be caused by both aerobic and anaerobic pathogens.

Prevention of primary manifestations: Treatment with G-CSF ameliorates symptoms and reduces infections in almost all affected individuals. Once absolute neutrophil count (ANC) levels normalize, resistance to infection greatly improves, such that affected individuals should be able to attend school, work, and recreational activities without specific concern. 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; routine immunizations.

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

Agents/circumstances to avoid: There is no need to avoid public places, as most infections are as a result of common organisms that occur on body surfaces.

Pregnancy management: Pregnancies in women with severe chronic neutropenia are at substantial risk for miscarriage; treatment with G-CSF may reduce this risk.

Evaluation of relatives at risk: Evaluate sibs and other at-risk relatives by molecular genetic testing for the *ELANE* pathogenic variant found in the proband to identify those with previously unrecognized mild or moderately severe disease who may benefit from treatment. Serial ANCs can also be used for evaluation of family members.

Genetic counseling

ELANE-related neutropenia is inherited in an autosomal dominant manner. One parent of a proband is usually affected. *De novo* pathogenic variants have been identified; their frequency is unknown. Each child of an individual with an *ELANE* pathogenic variant has a 50% chance of inheriting the variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the family-specific pathogenic variant is known.

GeneReview Scope

ELANE-Related Neutropenia: Included Phenotypes [1]
• Congenital neutropenia • Cyclic neutropenia

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

ELANE-related neutropenia represents a clinical spectrum that includes congenital neutropenia, cyclic neutropenia, and intermediate findings between these two phenotypes. Identification of the precise clinical phenotype is helpful for diagnosis, prognosis, and management.

Suggestive Findings

ELANE-related neutropenia **should be suspected** in individuals with the following clinical and supportive laboratory findings.

Clinical features

- **Severe or recurrent infections**
- **Congenital neutropenia.** Recurrent fevers, sinusitis, gingivitis, and chronic and severe infections in the lung, liver, and soft tissues occurring at irregular intervals
- **Cyclic neutropenia**
  - 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

Supportive laboratory findings

- **Congenital neutropenia**
  - At least three absolute neutrophil counts (ANCs) <500/μL obtained ≥3 months after birth supports the diagnosis.

    Note: The ANC is the white blood cell count (WBC) x % neutrophils.
  - ANCs are $<0.5x10^9$/L in most cases, and usually $<0.2x10^9$/L; in one series, the mean ANC was $0.112x10^9$/L.
  - 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.
  - Other hematopoietic cells
    - Monocyte counts tend to be increased (i.e., $>1.0x10^9$/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**
  - Most affected individuals have an ANC $<0.2x10^9$/L for three to five days at approximately three-week intervals.
  - 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.

Note: (1) Cyclic neutropenia is distinguished from congenital neutropenia by the regular oscillations of blood neutrophil counts in cyclic neutropenia. (2) 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.

Establishing the Diagnosis

A diagnostic algorithm for cyclic neutropenia has been published [Zeidler et al 2000].

The diagnosis of *ELANE*-related neutropenia **is established** in a proband by the identification of a heterozygous pathogenic variant in *ELANE* by molecular genetic testing (see Table 1).

Note: The distinction between cyclic neutropenia and congenital neutropenia is primarily based on clinical findings and only secondarily on genotype (see Genotype-Phenotype Correlations).

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

- **Single-gene testing.** Sequence analysis of *ELANE* is performed.

  Note: Since the presumed mechanism of disease is production of abnormal enzyme that is not inhibited or packaged normally resulting in damage to cells of the neutrophil lineage during their development, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

- **A multigene panel** that includes *ELANE* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Pathogenic variants in more than one gene associated with neutropenia have been identified in some individuals [Germeshausen et al 2010], but the clinical significance of finding variants in two or more neutropenia-associated genes is not known. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 *ELANE*-Related Neutropenia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ELANE	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Aprikyan et al [2002], Ancliff et al [2003b], Bellanné-Chantelot et al [2004]
5. 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.
6. Makaryan et al [2015]

Clinical Characteristics

Clinical Description

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 [Dale 2017, Skokowa et al 2017]. 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 [Dale 2017] (see Management).

Individuals with *ELANE*-related neutropenia are at risk of developing myelodysplasia syndrome (MDS) or acute myelogenous leukemia (AML). Myelodysplasia or leukemia typically arises gradually. The affected individual may have a gradual loss in response to G-CSF treatment or what appears to be a minor change in blood cell counts. If there is neutropenia, infections are likely to occur. Anemia may lead to fatigue. Annual bone marrow examinations with cytogenetic analysis are recommended for those treated with G-CSF. Chromosomal deletions, most commonly monosomy 7, are predictors for leukemic evolution; however, there may be a very long lag period, even many years, between the discovery of monosomy 7 and MDS/AML. Similarly, acquired pathogenic variants in *CSF3R* (the G-CSF receptor) and *RUNX1* predict evolution to leukemia, but clinical tests for these findings are not widely available or necessary in clinical practice [Skokowa et al 2017].

In a study conducted by Rosenberg et al [2008] the cumulative incidence of MDS/AML 15 years after starting treatment with G-CSF was 36%. This finding is similar to the cumulative incidence of MDS/AML 15 years after starting treatment with G-CSF in individuals with congenital neutropenia who do not have a pathogenic variant in *ELANE* (25%; $P = 0.96$) [Rosenberg et al 2006]. Similarly, 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 [Rosenberg et al 2010], although this study did not distinguish between individuals with *ELANE*-related neutropenia and those with congenital neutropenia as a result of other causes. 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 >8 µg/kg/day to achieve a mean neutrophil count equal to the group median [2.188×10^9/L]) were at greater risk of death from both sepsis and MDS/AML than those responding to lower doses [Rosenberg et al 2010, Makaryan et al 2015, Donadieu et al 2017].

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. Peak neutrophil counts are usually $<0.2 \times 10^9$/L. Variations in this classic pattern include cycles longer or shorter than three weeks (probably <5% of individuals) and reduced amplitude of oscillations. Counts in children tend to oscillate more obviously than in adults.

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 more than 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, probably because *ELANE* is expressed only in myeloid cells.

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 an affected individual has congenital or cyclic neutropenia.

Intermediate Phenotypes

Some affected individuals may at times have an obvious cyclic pattern of fluctuations in the neutrophil counts and at other times have counts that do not cycle, so that the diagnosis of congenital neutropenia seems appropriate. In families with multiple affected members in the same generation, one person may appear to have cyclic neutropenia while another has features more consistent with congenital neutropenia [Newburger et al 2010]. Cycling confers a favorable prognosis: better response to G-CSF and a lower risk of MDS/AML [Makaryan et al 2015, Dale et al 2017].

Genotype-Phenotype Correlations

Genotype-phenotype correlations are only roughly defined for *ELANE*-related neutropenia. Although the patterns of pathogenic variants in *ELANE*-associated cyclic neutropenia and congenital neutropenia are distinct on a population basis, the patterns of pathogenic variants do overlap, indicating that the distinction between cyclic neutropenia and congenital neutropenia is primarily based on clinical findings and only secondarily on genotype [Dale 2017, Skokowa et al 2017]. Newburger et al [2010] identified individuals with the same pathogenic variant who had different clinical phenotypes.

The risk of developing myelodysplasia or acute myelogenous leukemia varies considerably depending on the specific *ELANE* variant [Makaryan et al 2015]. The full scope of genotype-phenotype variation is not yet known, but the pathogenic variants p.Cys151Tyr and p.Gly214Arg variants are associated with a poor prognosis and the pathogenic variants p.Ser126Leu and p.Pro139Leu with a good prognosis.

Some *ELANE* pathogenic variants 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 pathogenic variants may be associated with severe congenital neutropenia and increased risk of AML [Bellanné-Chantelot et al 2004, Makaryan et al 2015]. At present it is not known how variations in the mutated protein affect the severity of neutropenia or the risk of AML.

Nomenclature

Prior to the discovery of the different genetic causes of severe chronic neutropenia, the term "Kostmann syndrome" was used to refer to individuals with severe chronic neutropenia. The original family reported by Kostmann was found to have bialleic pathogenic variants in *HAX1* inherited in an autosomal recessive fashion. However, one individual in a kindred originally described by Kostmann as having Kostmann syndrome was identified to have a pathogenic variant in *ELANE* [Zeidler & Welte 2002, Carlsson et al 2006] (see Differential Diagnosis).

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).

ELANE-related neutropenia is the most common cause of chronic neutropenia in children, although the precise prevalence of *ELANE*-related neutropenia is unknown.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Congenital Neutropenia

The differential diagnosis of congenital neutropenia includes the following disorders.

Isolated neutropenia

- Kostmann disease (OMIM 610738), an autosomal recessive form of severe congenital neutropenia caused by biallelic pathogenic variants in *HAX1* [Klein et al 2007]

  Note: *De novo* heterozygous *ELANE* pathogenic variants (autosomal dominant severe congenital neutropenia) are much more common than *HAX1* pathogenic variants (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.

- Nonsyndromic severe congenital neutropenia as a result of G6PC3 deficiency, an autosomal recessive form of severe congenital neutropenia caused by biallelic pathogenic variants in *G6PC3* (see G6PC3 Deficiency)

- *GFI1*-related severe congenital neutropenia. A heterozygous pathogenic variant in *GFI1* was reported in one person with severe congenital neutropenia [Person et al 2003].

- Benign familial neutropenia (OMIM 162700), an autosomal dominant form of congenital neutropenia with milder neutropenia and less severe symptoms

- Benign ethnic neutropenia associated with the Duffy null genotype (Duffy antigen receptor for chemokines or DARC-null genotype) is a common cause of neutropenia in persons of African heritage [Thobakgale & Ndung'u 2014]. This condition is caused by biallelic pathogenic variants in *ACKR1* and is inherited in an autosomal recessive fashion.

- Autoimmune neutropenia, usually attributed to anti-neutrophil antibodies

- Idiopathic neutropenia (isolated neutropenia of unknown cause)

- Cyclic neutropenia

Selected syndromes with congenital neutropenia (See Klein [2011].)

- Glycogen storage disease type Ib
- Shwachman-Diamond syndrome
- Reticular dysgenesis (OMIM 267500)
- Cartilage-hair hypoplasia
- Chediak-Higashi syndrome

- Griscelli syndrome (OMIM PS214450)
- Barth syndrome
- Wiskott-Aldrich syndrome (See *WAS*-Related Disorders.)
- Dyskeratosis congenita
- Myelokathexis (WHIM syndrome; OMIM 193670)
- Classic G6PC3 deficiency (severe congenital neutropenia type 4) (See G6PC3 Deficiency.)

Cyclic Neutropenia

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

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 if they have not already been completed:

- Dental examination for gingival and periodontal disease
- Evaluation (particularly of those with severe congenital neutropenia) by an otolaryngologist and a pulmonologist for chronic sinopulmonary inflammation and deep abscesses
- Evaluation of individuals with severe congenital neutropenia for evidence of myelodysplasia or leukemia with bone marrow aspirate and biopsy
- Consultation with a clinical hematologist, geneticist, and/or genetic counselor for specific clinical advice

Treatment of Manifestations

Fevers require prompt evaluation and empiric treatment until the source of the fever can be definitively identified, at which time targeted treatment may be possible:

- Initiation of broad-spectrum antibiotics is important, even lifesaving, when an affected individual has signs of serious infection, which may be caused by either aerobic or anaerobic pathogens. Coverage matching local patterns for infections in immunosuppressed individuals should initially be given for both aerobic and anaerobic organisms.
- Granulocyte colony-stimulating factor (G-CSF), given subcutaneously, should also be administered daily starting immediately to promote increased neutrophil production and deployment.

Fever with abdominal pain is potentially life threatening because of the risk for peritonitis from a perforated colonic ulcer. Surgical evaluation by physical examination and (as needed) imaging studies is indicated.

Prevention of Primary Manifestations

Granulocyte colony-stimulating factor (G-CSF). Treatment with 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 granulocyte-macrophage (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 2017].

Treatment of cyclic neutropenia requires daily or alternate-day injections of G-CSF, normally in a dose of ~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, headache, splenomegaly, and osteoporosis. Vasculitis, rashes, arthralgias, and glomerulonephritis have been infrequently reported [Dale et al 2003].

Note: (1) When affected individuals are given G-CSF and their ANC normalizes, their resistance to infection improves greatly. They should be able to attend school, work, and engage in recreational activities without specific concerns; (2) G-CSF treatment is associated with mild increases in the size of the spleen, but this is very rarely, if ever, a cause for specific concern in those with *ELANE*-related neutropenia.

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, Connelly et al 2012, Fioredda et al 2015].
- 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.

Individuals with *ELANE*-associated neutropenia are susceptible to common viral infections that may be complicated by bacterial infections, such as pneumonia as a result of bacteria commonly found in the upper respiratory tract. Such individuals respond well to immunizations to protect them from viral and bacterial infections. They should be given all routine vaccines.

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 (*CSF3R*) from peripheral blood may also provide evidence of evolution to MDS/AML [Ancliff et al 2003a], its clinical utility is not yet clearly established [Touw 2015, Skokowa et al 2017].

Agents/Circumstances to Avoid

Most infections are caused by common organisms on body surfaces including *Clostridia* species and other anaerobes in the intestinal biota. For this reason it is of little or no benefit to avoid public places.

Evaluation of Relatives at Risk

Evaluation of sibs and other at-risk relatives by molecular genetic testing for the *ELANE* pathogenic variant found in the proband identifies those with previously unrecognized mild or moderately severe disease who may benefit from treatment. Serial ANCs can also be used for evaluation of family members.

Note: Relatives of individuals with typical cycles may have neutropenia but lack obvious cycles.

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 2015]. Of these 88 women, 44 had congenital or cyclic neutropenia – accounting for 95 of the 183 pregnancies. Although genetic testing results were not reported, it is likely that at least half of the 44 women had *ELANE*-related neutropenia. In general the health of all the infants was equivalent for the two groups. Other findings included the following:

- Reduced risk of fetal loss in the women treated during pregnancy
- Among 55 women (123 pregnancies) not treated with G-CSF during pregnancy: 11 complications (1 premature rupture of membranes, 2 life-threatening infections, 2 minor infections, and 6 premature labors)
- Among 41 women (60 pregnancies) treated with G-CSF during pregnancy: no life-threatening infections, no premature labors, five minor infections, and one woman who developed severe thrombocytopenia

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Unrelated cord blood transplantation for neutropenia is being investigated; outcome appears to depend on the closeness of the match [Connelly et al 2012, Fioredda et al 2015].

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

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.
- Some individuals diagnosed with *ELANE*-related neutropenia have the disorder as the result of a *de novo* *ELANE* pathogenic variant. *De novo* pathogenic variants have been identified [Horwitz et al 1999, Aprikyan et al 2002]; their frequency is unknown.
- If neither parent is known to be affected, molecular genetic testing of the parents for the *ELANE* pathogenic variant identified in the proband is recommended. Parents may also be evaluated with complete blood counts (CBCs) obtained weekly for a month until an ANC $<0.2 \times 10^9$/L is documented in more than one sample.
- If the 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 [Newburger et al 2010].
- 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 a pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to sibs of the proband depends on the genetic status of the parents.
  - If a parent of the proband is affected or has the pathogenic variant, the risk to sibs is 50%.
  - If the *ELANE* pathogenic variant 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].
- If the parents have not been tested for the *ELANE* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low; however, parental germline mosaicism remains a possibility.

Offspring of a proband. Each child of an individual with *ELANE*-related neutropenia has a 50% chance of inheriting the *ELANE* pathogenic variant.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents: if a parent has the *ELANE* pathogenic variant, the parent's family members are at risk.

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 or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored. Multiple cases of *ELANE*-related neutropenia have occurred via sperm donation from a single donor [Boxer et al 2006].

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ELANE* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

- **National Neutropenia Network**
  Phone: 866-600-0799
  Email: stephanie@neutropenianet.org
  www.neutropenianet.org
- **Neutropenia Support Association Inc.**
  Canada
  Phone: 800-6-NEUTRO (638876); 204-781-7240
  Email: stevensl@neutropenia.ca
  www.neutropenia.ca
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**
  Phone: 800-518-8474
  Email: NCI.IBMFS@westat.com
  www.marrowfailure.cancer.gov
- **Severe Chronic Neutropenia International Registry**
  Phone: 49-511-557105
  Fax: 49-511-557106
  Email: SCNIR@mh-hannover.de
  Severe Chronic Neutropenia International Registry

Molecular Genetics

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

Table A. ELANE-Related Neutropenia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ELANE	19p13.3	Neutrophil elastase	CCHMC - Human Genetics Mutation Database (ELANE) ELA2base: Mutation registry for Cyclic and congenital neutropenia (ELANE)	ELANE	ELANE

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 ELANE-Related Neutropenia (View All in OMIM)

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

Molecular Pathogenesis

Neutrophils are an essential part of the innate immune system and, therefore, are required to produce enzymes that are cytotoxic by nature. *ELANE* encodes leukocyte elastase (or neutrophil elastase), which is packaged into neutrophil granules as fully active enzyme. The cell is normally protected from damaging enzyme activity by the terminal peptides that are cleaved just before packaging; however, in congenital neutropenia and cyclic neutropenia, the abnormal enzyme is not inhibited or packaged normally and, therefore, damages cells of the neutrophil lineage during their development.

Gene structure. The gene comprises five exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *ELANE* pathogenic variants include missense and nonsense variants, 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 pathogenic variants and 94 of 105 probands with cyclic neutropenia were heterozygous for seven different pathogenic variants [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.

Table 2. Selected *ELANE* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.211T>C	p.Cys71Arg	NM_001972.2 NP_001963.1
c.377C>T	p.Ser126Leu	
c.416C>T	p.Pro139Leu	
c.452G>A	p.Cys151Tyr	
c.640G>C	p.Gly214Arg	

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.

Normal gene product. *ELANE* encodes leukocyte elastase (also called neutrophil elastase), a 240-amino-acid protein with broad proteolytic activities, which is processed into a 238-amino-acid mature protein. Leukocyte

elastase, produced by neutrophil precursors, is an early developmental feature of the neutrophil's primary granules. The enzyme is processed in the Golgi apparatus and packaged into the granules as fully active enzyme [Garwicz et al 2005]. The cell is normally protected from damaging enzyme activity by the terminal peptides that are cleaved just before packaging.

Abnormal gene product. It is hypothesized that in congenital neutropenia and cyclic neutropenia the abnormal enzyme is not inhibited or packaged normally and, therefore, damages cells of the neutrophil lineage during their development.

A natural experiment has provided compelling evidence that pathogenic variants in *ELANE* result in the destruction of neutrophils before they can enter circulation. The father of an individual with congenital neutropenia was found to be mosaic for a c.211T>C (p.Cys71Arg) pathogenic variant; half of his somatic cells tested contained the abnormal 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. 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, Köllner et al 2006, Skokowa et al 2017].

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Chapter Notes

Revision History

- 23 August 2018 (ma) Comprehensive update posted live
- 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 live
- 13 September 2005 (dd) Revision: Genotype-Phenotype Correlations, Surveillance
- 21 May 2004 (me) Comprehensive update posted live
- 1 October 2003 (cd) Revision: clinical testing availability
- 17 June 2002 (me) Review posted live
- 21 September 2001 (dd) Original submission

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