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G6PC3 Deficiency

Synonym: Ubiquitous Glucose-6-Phosphatase Deficiency

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Summary

Clinical characteristics

G6PC3 deficiency is characterized by severe congenital neutropenia which occurs in a phenotypic continuum that includes the following:

- Isolated severe congenital neutropenia (nonsyndromic)
- Classic G6PC3 deficiency (severe congenital neutropenia plus cardiovascular and/or urogenital abnormalities)
- Severe G6PC3 deficiency (classic G6PC3 deficiency plus involvement of non-myeloid hematopoietic cell lines, additional extra-hematologic features, and pulmonary hypertension; known as Dursun syndrome)

Neutropenia usually presents with recurrent bacterial infections in the first few months of life. Intrauterine growth restriction (IUGR), failure to thrive (FTT), and poor postnatal growth are common. Other findings in classic and severe G6PC3 deficiency can include inflammatory bowel disease (IBD) resembling Crohn disease, and endocrine disorders (growth hormone deficiency, hypogonadotropic hypogonadism, and delayed puberty).

Diagnosis/testing

The diagnosis of G6PC3 deficiency is established in a proband with severe congenital neutropenia and biallelic (homozygous or compound heterozygous) *G6PC3* pathogenic variants on molecular genetic testing.

Management

Treatment of manifestations: Treatment with granulocyte colony stimulating factor (G-CSF) that maintains absolute neutrophil counts above 0.5×10^9/L reduces the number of infections and improves the quality of life. A few mildly affected individuals have been reported to be adequately managed with prophylactic antibiotics alone. Fevers and infections require prompt treatment with antibiotics. Routine management of congenital heart disease, renal and urinary tract malformations, and hormone deficiencies as needed.

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Prevention of secondary complications: Good dental hygiene, including careful brushing and flossing and regular visits to the dentist, helps decrease the potential for infection. Prophylactic antibiotics should be considered in those with uncorrected neutropenia undergoing dental procedures, especially in those with heart defects at increased risk for subacute bacterial endocarditis.

Surveillance: Frequent follow up by a hematologist or immunologist to monitor infection frequency and neutrophil counts to ensure an adequate response to G-CSF. Monitor growth in children, pubertal development in adolescents, and development of varicose veins, especially in adults. Monitoring for osteopenia/osteoporosis.

Evaluation of relatives at risk: It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early diagnosis and management of the hematologic, cardiac, renal, and endocrine abnormalities of G6PC3 deficiency. The genetic status of at-risk sibs can be clarified by molecular genetic testing (if the *G6PC3* pathogenic variants in the family are known) or by clinical findings.

Genetic counseling

G6PC3 deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *G6PC3* pathogenic variants have been identified in the family.

GeneReview Scope

G6PC3 Deficiency: Included Phenotypes
• Nonsyndromic severe congenital neutropenia due to G6PC3 deficiency • Classic G6PC3 deficiency (severe congenital neutropenia type 4) • Severe G6PC3 deficiency (Dursun syndrome)

Diagnosis

Consensus diagnostic criteria for G6PC3 deficiency have not been established.

Suggestive Findings

G6PC3 deficiency should be suspected in individuals with the following:

- Severe congenital neutropenia defined as an absolute neutrophil count <0.5 x 10^9/L which usually results in early-onset, frequent, severe bacterial infections

  Note: Although maturation arrest of myeloid cells was initially thought to be the typical finding on bone marrow examination [Boztug et al 2009], subsequent reports identified bone marrows that were hypercellular [McDermott et al 2010] and normocellular [Banka et al 2011b]. More recently, sequential bone marrow examinations have typically revealed normal maturation and only rarely arrested maturation [Desplantes et al 2014].

- A family history consistent with autosomal recessive inheritance [Banka & Newman 2013]

To date all individuals with G6PC3 deficiency have had severe congenital neutropenia; the phenotypic spectrum is a continuum that ranges from nonsyndromic (isolated severe congenital neutropenia) to classic (severe congenital neutropenia plus cardiovascular and/or urogenital abnormalities) to severe (classic G6PC3 deficiency plus involvement of non-myeloid hematopoietic cell lines and additional extra-hematologic features).

Nonsyndromic G6PC3 deficiency includes only hematologic findings –predominantly severe congenital neutropenia [Smith et al 2012, Banka et al 2013].

Classic G6PC3 deficiency (known as severe congenital neutropenia type 4) includes severe congenital neutropenia as well as additional features [Boztug et al 2009, Banka et al 2011a, Boztug et al 2012]:

- Other hematologic abnormalities: intermittent thrombocytopenia (66%)
- Cardiovascular defects
  - Congenital heart defects (~77%) (See Clinical Description.)
  - Prominent superficial venous pattern (66%) which may not be visible at birth but tends to gradually develop with age
- Urogenital defects (44%), especially in males in whom cryptorchidism is the most common anomaly

Severe G6PC3 deficiency (Dursun syndrome) comprises the findings of classic G6PC3 deficiency as well as additional features:

- Primary pulmonary hypertension (PPH) developing in the newborn period
- Non-myeloid cell involvement: severe lymphopenia
- Thymic hypoplasia

Establishing the Diagnosis

The diagnosis of G6PC3 deficiency is established in a proband with severe congenital neutropenia and biallelic (homozygous or compound heterozygous) *G6PC3* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *G6PC3* variants of uncertain significance (or of one known *G6PC3* pathogenic variant and one *G6PC3* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *G6PC3* followed by consideration of deletion/duplication analysis if only one or no pathogenic variant is found. It should be noted that to date no exon or whole-gene deletions/duplications have been reported.

- **A multigene panel** that includes *G6PC3* and other genes of interest (see Differential Diagnosis) may also be considered. Note: The genes included and sensitivity of multigene panels vary by laboratory and over time.

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

- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of G6PC3 deficiency.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in G6PC3 Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
G6PC3	Sequence analysis [3]	16/31 (43%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. An estimate based on a single nonsystematic study in which Boztug et al [2012] sequenced *G6PC3* in individuals with syndromic forms of congenital neutropenia.
5. To date more than 91 individuals with molecularly confirmed G6PC3 deficiency have been reported [Alangari et al 2013, Banka & Newman 2013, Estévez et al 2013, Racek et al 2013, Desplantes et al 2014, Kaya et al 2014, Notarangelo et al 2014, Ozgül et al 2014, Tavil et al 2014, Yeshayahu et al 2014, Arikoglu et al 2015, Lebel et al 2015].
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

G6PC3 deficiency is highly variable in its severity and associated clinical features. Individuals with "nonsyndromic" disease have only severe congenital neutropenia. The majority of persons with G6PC3 deficiency have cardiovascular and/or urogenital features (so-called classic G6PC3 deficiency). Of those with classic disease, a subset are more severely affected (so-called Dursun syndrome) because of the additional involvement of myeloid cells, primary pulmonary hypertension developing in the newborn period, and minor dysmorphic features.

While it is estimated that nearly 10% of G6CP3 deficiency is the nonsyndromic form, this could be an underestimate due to ascertainment bias (i.e., selection of more severe phenotypes for testing of *G6PC3* in previous studies) [Banka & Newman 2013]. It is also possible that some individuals who initially present with the nonsyndromic form may develop features of the classic form in later life [Notarangelo et al 2014].

G6PC3 deficiency usually presents in the first few months of life with recurrent bacterial infections. A range of bacterial infections have been reported [Desplantes et al 2014]; respiratory tract infections, otitis media, stomatitis, urinary tract infections, pyelonephritis, skin abscesses, cellulitis, and sepsis are particularly common. The first serious infection can occur at any age, ranging from immediately after birth to adulthood.

Hematologic. Persistent severe neutropenia is present in all affected individuals and is the core phenotype of the condition.

Intermittent thrombocytopenia is seen frequently but usually does not cause symptoms.

Lymphopenia associated with hypoplasia of the thymus can be seen in more severely affected individuals [Dursun et al 2009, Banka et al 2010, Ozgül et al 2014].

Cardiovascular. Congenital heart defects are common. In their recent review, Banka & Newman [2013] found that 44 (77%) of 57 of individuals with G6PC3 deficiency described in the literature had congenital cardiac defects. By far the most common anomaly was atrial septal defect. Other rare heart anomalies include patent foramen ovale; cor triatriatum; patent ductus arteriosus; critical pulmonary stenosis and hypoplastic left

ventricle; mitral valve prolapse, insufficiency, and/ or regurgitation; tricuspid insufficiency; and bicuspid aortic and pulmonary valves.

A prominent superficial venous pattern begins to emerge between late infancy and early childhood in most affected children [Banka et al 2011a]. This pattern can be seen on the trunk, extremities, and sometimes on the head. Experience with adults is limited but older individuals have a tendency to develop varicose veins and venous ulcers.

In Dursun syndrome early-onset primary pulmonary hypertension can be difficult to control [Dursun et al 2009]. In a few individuals primary pulmonary hypertension may be detected later in life [McDermott et al 2010, Fernandez et al 2012].

Urogenital anomalies are more common in males than females [Banka & Newman 2013]. In males the most common feature is cryptorchidism.

Hydronephrosis, poor renal cortico-medullary differentiation, small kidneys, and vesico-uretric reflux are observed in some affected individuals. Other features include inguinal hernia, ambiguous genitalia in undervirilized males, and urachal fistula.

Inflammatory bowel disease (IBD) resembling Crohn disease has been described in a few individuals [Cullinane et al 2011, Fernandez et al 2012, Smith et al 2012, Bégin et al 2013, Desplantes et al 2014, Kaya et al 2014]. Treatment that improves neutrophil counts can also help resolve the bowel disease [Kaya et al 2014].

Endocrine. Growth hormone deficiency has been described in two affected individuals [Boztug et al 2012].

Hypogonadotropic hypogonadism and delayed puberty have been reported in both males and females [Germeshausen et al 2010, Banka et al 2011a, Boztug et al 2012, Aytekin et al 2013]. One male, who had no detectable gonadal structures in the scrotum, inguinal canals, or abdomen, had a low testosterone level (unresponsive to HCG stimulation) and extremely high LH and FSH levels [Yeshayahu et al 2014].

Hypothyroidism has been reported in three individuals [Banka et al 2011a, Desplantes et al 2014].

Growth. Intrauterine growth restriction (IUGR), failure to thrive (FTT), and poor postnatal growth are common. The basis of growth problems is not known. It could be secondary to repeated infections or part of the primary phenotype of G6PC3 deficiency.

Other findings

- Minor dysmorphic features in some young children, such as a triangular face, depressed nasal bridge, thick lips, and prognathism [Dursun et al 2009, Banka et al 2011a, Boztug et al 2012, Desplantes et al 2014]
- Neurodevelopmental involvement:
  - Mild learning difficulties were initially described in four affected individuals from a single family [Banka et al 2011a], although it was not clear whether the findings were attributable to G6PC3 deficiency.
  - Recently a study from the French Neutropenia Registry reported neurodevelopmental difficulties in seven of 14 individuals with pathogenic variants in *G6CP3*. Notably, one was said to have major developmental problems with bilateral atrophy on MRI [Desplantes et al 2014].
- Skeletal involvement, such as scoliosis and pectus carinatum [Dursun et al 2009, Boztug et al 2012]
- Cutis laxa, described in at least seven individuals [Boztug et al 2012, Desplantes et al 2014]
- Microcephaly [Boztug et al 2009, Germeshausen et al 2010, McDermott et al 2010], which could be an effect of overall poor growth
- Myopathy:
  - One individual with a single episode of myositis [Smith et al 2012]

- One sib pair with proximal muscle weakness [McDermott et al 2010], one of whom developed at age 2.5 years recurrent episodes of proximal muscle pain and cramps; muscle histology suggested glycogen accumulation.
- Two individuals reported with nonspecific myopathy but no clinical details [Boztug et al 2009, Desplantes et al 2014]

Rarer features (some of which could be coincidental associations)

- Myelodysplasia followed by acute myelogeneous leukemia with translocation (18, 21) (with no exposure to G-CSF) reported in one affected individual age 14 years [Desplantes et al 2014]
- Mild to moderate bilateral sensorineural hearing loss which may be asymptomatic and is sometimes only detected on audiometry [McDermott et al 2010, Gatti et al 2011, Boztug et al 2012, Desplantes et al 2014]. The age of onset is not clear from the published reports.
- Congenital ptosis [Boztug et al 2012]
- Cleft palate [Boztug et al 2009] and Pierre Robin sequence [Desplantes et al 2014].
- Low HDL serum levels and persistently increased amylase activity described in one individual [Banka et al 2011a]

Disease course. When neutropenia is treated (see Management), most affected individuals have a good prognosis with reduced rate and severity of infections.

If neutropenia is untreated, G6PC3 deficiency can lead to death in early childhood from infections [Alizadeh et al 2011] or severe respiratory distress [Dursun et al 2009]. One adult who was noncompliant with treatment died at age 37 years of bacterial endocarditis [Fernandez et al 2012].

Four deaths in the 14 individuals in the French Severe Congenital Neutropenia Registry were reported: one at age five years with sepsis, one at age 19 years from pulmonary insufficiency, and two from sudden death of unknown cause during sleep at age 30 years.

Genotype-Phenotype Correlations

No obvious genotype-phenotype correlations explain the difference between the marked cellularity of myeloid cells in the bone marrow of individuals with G6PC3 deficiency [Banka et al 2011b].

Based on limited data, certain pathogenic variants (e.g., p.Phe44Ser) appear to be more often (or only) associated with nonsyndromic neutropenia [Banka et al 2013].

Prevalence

To date more than 91 individuals with the molecularly proven diagnosis of G6PC3 deficiency have been reported [Alangari et al 2013, Banka & Newman 2013, Estévez et al 2013, Racek et al 2013, Desplantes et al 2014, Kaya et al 2014, Notarangelo et al 2014, Ozgül et al 2014, Tavil et al 2014, Yeshayahu et al 2014, Arikoglu et al 2015, Lebel et al 2015].

The prevalence is likely to vary significantly from population to population based on the presence of founder variants in certain populations [Smith et al 2012, Banka & Newman 2013] and cultural practices such as consanguinity. For example, G6PC3 deficiency was the most common cause of severe congenital neutropenia in Israel, accounting for the diagnosis in 25% of individuals [Lebel et al 2015].

The French Neutropenia Registry has estimated incidence at birth at 0.4:1,000,000 [Desplantes et al 2014].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *G6PC3*.

Differential Diagnosis

Severe congenital neutropenia is genetically heterogeneous [Klein 2009, Donadieu et al 2011, Klein 2011]. The differential diagnosis of G6PC3 deficiency can be divided into inherited conditions in which neutropenia predominates and those in which neutropenia may be a part of a multisystem disorder.

Inherited Conditions in which Neutropenia Predominates

Severe congenital neutropenia type 1 (SCN1), an autosomal dominant disorder caused by mutation of *ELANE*, is the most common genetic cause of congenital neutropenia. *ELANE*-related congenital neutropenia is characterized by recurrent fever, skin and oropharyngeal inflammation (i.e., mouth ulcers, gingivitis, sinusitis, and pharyngitis), and cervical adenopathy [Dale et al 2000]. Mutation of *ELANE* also causes cyclic neutropenia, a less severe disorder.

Severe congenital neutropenia type 2 (SCN2) (OMIM 613107), an autosomal dominant disorder caused by mutation of *GFI1,* is characterized by an increased susceptibility to bacterial infections [Person et al 2003]. Mutation of *GFI1* also causes chronic non-autoimmune neutropenia which manifests as monocytosis in adults.

Kostmann disease (severe congenital neutropenia type 3) (OMIM 610738), an autosomal recessive disorder caused by mutation of *HAX1,* is characterized by neutropenia, maturation arrest of the promyelocyte or myelocyte stage with or without seizures, and developmental delay [Klein et al 2007].

Severe congenital neutropenia type 5 (SCN5) (OMIM 615285), an autosomal recessive disorder caused by mutation of *VPS45,* is characterized by neutropenia, neutrophil dysfunction, bone marrow fibrosis, and nephromegaly resulting from renal extramedullary hematopoiesis [Vilboux et al 2013].

Severe congenital neutropenia, X-linked (XLN), caused by mutation of *WAS,* is characterized in males by recurrent bacterial infections, persistent neutropenia, and arrested development of the bone marrow at the promyelocyte/myelocyte stage in the absence of other clinical findings of Wiskott-Aldrich syndrome.

***JAGN1*-related severe congenital neutropenia (severe congenital neutropenia type 6)** (OMIM 616022), an autosomal recessive disorder, is characterized by severe congenital neutropenia, increased susceptibility to bacterial infections, maturation arrest at the promyelocyte/myelocyte stage in the bone marrow, and poor response to treatment with human granulocyte colony-stimulating factor (rhG-CSF) [Boztug et al 2014]. Occasionally abnormalities are observed in bone, pancreas, and/or teeth.

Inherited Conditions in which Neutropenia May be Part of a Multisystem Disorder

- Barth syndrome
- Cartilage-hair hypoplasia
- Charcot-Marie-Tooth disease caused by mutation of *DNM2* (OMIM 606482)
- Chediak-Higashi syndrome
- Clericuzio poikiloderma with neutropenia
- Cohen syndrome
- Glycogen storage disease type 1b
- Griscelli syndrome type 2 (OMIM 607624)

- Hermansky-Pudlak syndrome type 2
- Immunodeficiency due to defect in MAPBP-interacting protein (P14 deficiency) (OMIM 610798)
- Pearson syndrome
- Shwachman-Diamond syndrome
- WHIM syndrome (OMIM 193670)
- Wiskott-Aldrich syndrome

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with G6PC3 deficiency, the following evaluations are recommended:

- Full blood count to look for evidence of other hematologic involvement (i.e., intermittent thrombocytopenia and/or lymphopenia)
- Immunologic evaluation for T-cell subsets in individuals with a more severe presentation and unusual non-bacterial infections
- Consultation with a cardiologist to evaluate for congenital heart disease
- Renal and pelvic ultrasound examination to look for urogenital malformations
- Growth parameters in children and pubertal development in adolescents
- Age appropriate endocrine assessment for evidence of the hormone deficiencies reported (i.e., growth hormone, gonadotropins, thyroid hormone)
- Biochemical investigations to look for abnormalities in the lipid profile
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Neutropenia. Treatment with granulocyte colony stimulating factor (G-CSF) improves neutrophil numbers, reduces the number of infections, and improves the quality of life [Boztug et al 2009, McDermott et al 2010, Boztug et al 2012]. Of note, the dose required to keep absolute neutrophil counts above $0.5x10^9$/L can vary greatly among affected individuals. In some individuals G-CSF – even in large doses – may fail to control infections [Smith et al 2012].

A few mildly affected individuals have been reported to be adequately managed with prophylactic antibiotics alone [Banka et al 2013]. However, prophylactic antibiotics have a limited use for preventing severe infections or bronchiectasis and inflammatory bowel disease.

Fevers and infections require prompt treatment with antibiotics.

Other

- Routine management of congenital heart disease, renal and urinary tract malformations
- Routine management of hormone deficiencies
- Consideration of oral steroids for inflammatory bowel disease [Desplantes et al 2014] or anti-TNF treatment [Bégin et al 2013]. Some complications of IBD such as bowel stenosis may require appropriate surgical intervention.
- Consideration of pancreatic enzyme supplementation if steatorrhea is present [Desplantes et al 2014]
- Chemotherapy and hematopoietic stem cell transplantation for acute myelogeneous leukemia

Prevention of Secondary Complications

Good dental hygiene, including careful brushing and flossing and regular visits to the dentist, helps decrease the potential for infection. Prophylactic antibiotics should be considered with dental procedures, including routine dental repair and cleaning, especially in individuals with heart defects.

Surveillance

The following are appropriate:

- Frequent follow up by a hematologist or immunologist to monitor infection frequency and neutrophil counts to ensure an adequate response to G-CSF (i.e., absolute neutrophil counts above 0.5x109/L)
- Monitoring of growth in children and pubertal development in adolescents
- Biochemical profile including lipid profile
- Monitoring for development of varicose veins, especially in adults
- Monitoring for osteopenia/osteoporosis

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early diagnosis and management of the hematologic, cardiac, renal, and endocrine abnormalities of G6PC3 deficiency.

- If the *G6PC3* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the *G6PC3* pathogenic variants in the family are not known, the following evaluations can be used to help clarify the disease status of at-risk sibs: full blood count, bone marrow examination (if persistent severe neutropenia is detected on full blood count), directed general examination for prominence of superficial veins, echocardiogram, and renal and pelvic ultrasound examination.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

G6PC3 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *G6PC3* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of the sib being a carrier of a *G6PC3* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with G6PC3 deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *G6PC3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *G6PC3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *G6PC3* pathogenic variants in the family.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *G6PC3* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for G6PC3 deficiency are possible.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Neutropenia Network**
  Phone: 866-600-0799
  Email: jeanne@neutropenianet.org
  neutropenianet.org

- **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
  marrowfailure.cancer.gov
- **Severe Chronic Neutropenia International Registry**
  Phone: 49-511-557105
  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. G6PC3 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
G6PC3	17q21.31	Glucose-6-phosphatase 3	G6PC3 database	G6PC3	G6PC3

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 G6PC3 Deficiency (View All in OMIM)

611045	GLUCOSE-6-PHOSPHATASE, CATALYTIC, 3; G6PC3
612541	NEUTROPENIA, SEVERE CONGENITAL, 4, AUTOSOMAL RECESSIVE; SCN4

Molecular Pathogenesis

G6PC3 deficiency causes decreased cytoplasmic glucose and glucose-6-phosphate levels [Jun et al 2012] that lead to activation of GSK-3β and phosphorylation-mediated inactivation of the anti-apoptotic molecule Mcl-1. Activation of the endoplasmic reticulum stress mechanism and increased susceptibility to cellular apoptosis has been demonstrated [Boztug et al 2009, Jun et al 2011]. G6PC3 deficiency also results in aberrant glycosylation of a NADPH oxidase subunit, gp91phox leading to deficits in neutrophil function.

Gene structure. *G6PC3* consists of six exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *G6PC3* pathogenic variants include missense, nonsense, and splice-site variants and frameshift deletions or insertions. Pathogenic missense variants generally lead to non-conservative substitutions at highly conserved residues.

A number of founder variants have been identified, including:

- p.Phe44Ser in individuals of Pakistani origin [Smith et al 2012];
- p.Arg253His in individuals from diverse backgrounds in the Middle East [Banka et al 2011a];
- p.Gly260Arg in individuals with European ancestry [Banka & Newman 2013].

Other pathogenic variants detected in two or more unrelated individuals of the same ancestry include p.Phe71SerfsTer46 ("Hispanic"), p.Gly277Ter (European), and p.Asn313GlnfsTer74 (Iranian) [Banka & Newman 2013].

Table 2. *G6PC3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.130C>T	p.Phe44Ser	NM_138387.3 NP_612396.1
c.210delC	p.Phe71SerfsTer46 (Ile70fsTer46)	
c.758G>A	p.Arg253His	
c.778G>C	p.Gly260Arg	
c.829C>T	p.Gly277Ter	
c.935dupT	p.Asn313GlnfsTer74 (Asn313fs)	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. G6PC3 is found in the endoplasmic reticulum and comprises 346 amino acid residues. The signature phosphatase motif is between residues 66 and 171.

Abnormal gene product. It is predicted that missense variants destabilize the mutated protein and truncating variants lead to nonsense-mediated decay of the transcript or the generation of abnormal gene product [Banka & Newman 2013].

Chapter Notes

Revision History

- 16 April 2015 (me) Review posted live
- 10 September 2014 (sb) Original submission

References

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