CGD ASSOCIATION OF AMERICA

WHAT YOU NEED TO KNOW

A GUIDE FOR CARRIERS OF X-LINKED CHRONIC GRANULOMATOUS DISEASE

Chronic Granulomatous Disease (CGD) is a rare, immune deficiency disorder that is caused by inherited defects in an important enzyme in white blood cells that manufactures oxidants for microbial killing. The disorder is characterized by an inability to resist potentially life-threatening infections caused by certain types of bacteria and fungal species and a tendency to develop chronic inflammation. CGD can also be associated with the development of granulomatous lesions of the skin, lungs, bones, and lymph nodes formed by collections of inflammatory white blood cells.

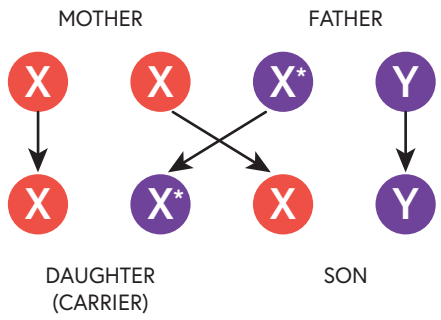
CGD is an inherited condition and can be passed down in either an X-linked or autosomal recessive pattern. Out of all affected individuals, two-thirds have the X-linked form of the disorder. For X-linked CGD, males are most severely affected and females are considered carriers and have a 50% chance of passing CGD down to any children they have. For autosomal recessive CGD, both parents must be carriers in order to pass CGD down to a child. If both parents are carriers, there is a 25% chance their child will have CGD, a 50% chance their child will be a carrier, and a 25% chance their child will be healthy.

This guide focuses on carriers of X-linked CGD, who may experience symptoms of the condition.

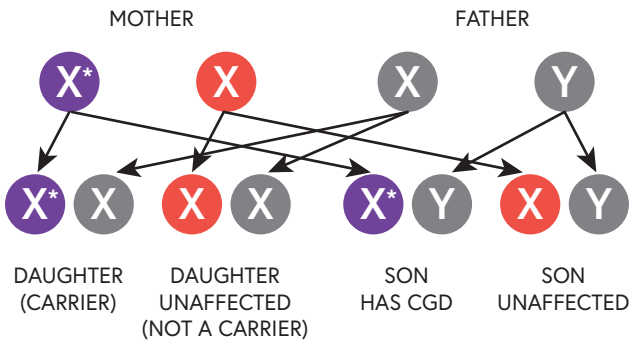
Included in this guide:

- Family Planning
- Communicating carrier risk with family members
- Genetic Testing
- Self Advocacy
- Symptoms
- Diagnosing CGD carrier status
- Symptoms
- Mental Health
- References and Resources

Carrier daughter inheritance from father:



X-linked CGD inheritance from mother:



Source: CGD Society; https://cgdsociety.org/about-cgd/inheritance/

Family Planning

When planning a family, it is important to consider X-linked Chronic Granulomatous Disease (CGD) carrier status as female carriers of X-linked CGD have a 50 percent chance of passing down the genetic defect to their children. Every son born to a female carrier of CGD will have a 50 percent chance of having CGD; every daughter will have a 50 percent chance of being a carrier of the disease. If a male with CGD has a daughter, there is a 100 percent chance that she will be a carrier of CGD; his sons will be free of CGD.

Given the inheritance pattern of X-linked CGD, carriers have important decisions to make when it comes to family planning. These decisions may involve financial, moral, ethical, and practical considerations. There is no right or wrong path when it comes to making these very personal determinations. It is highly recommended that CGD carriers meet with a genetic counselor to discuss their options before having children. These options may include the following:

In vitro fertilization with preimplantation genetic testing (IVF with PGT): Some families choose to pursue preimplantation genetic testing via in vitro fertilization. This involves testing embryos for the known genetic defect that causes X-linked CGD and choosing to only implant embryos that do not contain the defect for pregnancy. This is also a procedure that carriers may consider to conceive a child that is an HLA match and may be able to donate cord blood or stem cells for an ill sibling.

Prenatal testing: Prenatal genetic testing is available to families who wish to learn more about their unborn child's risk for X-linked CGD. This testing involves invasive procedures such as chorionic villus sampling or amniocentesis to determine whether the fetus is affected with the condition. Families choose to pursue prenatal diagnostic testing for many different reasons, including to gather information to better prepare for the child's medical management or to consider termination of the pregnancy.

Donor egg: As a female CGD carrier has a 50% chance of having an affected son, some carriers choose to bypass this risk by utilizing an egg donated by another woman to ensure that the genetic defect will not be passed on.

Natural conception without prenatal testing: Some carriers choose to conceive naturally and forgo diagnostic genetic testing during a pregnancy. There are postnatal options to learn whether the child carries the X-CGD genetic defect, such as cord blood testing after birth or testing of the child after birth.

Communicating carrier risk to daughters and other female family members

Telling female family members, such as daughters, cousins or even mothers and grandmothers, that they may be carriers of CGD may be difficult and involve complex conversations. However, with professional guidance, intra-family communication can be very beneficial to the health and wellbeing of potential CGD carriers.

It is strongly recommended that females who are known or potential carriers of X-linked CGD meet with a genetic counselor to discuss their health management as well as their reproductive options where applicable. Genetic counselors can help individuals of many ages and education levels understand both their own risk for disease and their risk of passing the disease to their children based on their genetics. They can also advise carriers how to explain their carrier status to family members, as well as how to alert female relatives that they, too, could be carriers.

A genetic counselor may suggest, for example, that in explaining carrier status to younger family members or to those who do not have a good understanding of genetics and modes

of inheritance, analogies can be useful in helping to portray genetic risk. For example, a CGD carrier might use the flip of a coin to demonstrate to her daughter that there is a 50 percent chance that she has inherited the mutated gene, thereby enabling her daughter to better understand her risk of being a carrier. These difficult conversations can provoke a variety of emotions, and it is appropriate to seek out professional support where needed.

Genetic counselors can help individuals understand both their own risk for disease and their risk of passing the disease to their children based on their genetics.

Genetic testing to determine carrier status

Female family members who are at risk for being CGD carriers may wish to pursue genetic testing to determine whether or not they have in fact inherited the mutated gene responsible for CGD, particularly if they are of child-bearing age and are capable of passing on the disease. Where the potential carrier is a child, the determination as to whether and/or when carrier testing should be performed is a very personal one, with some parents choosing to have their daughters tested at a young age, and others waiting until their daughter reaches the age of majority and can make the decision herself. Some medical organizations such as the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) do not recommend routine carrier testing in minors when there are no health benefits in childhood. However, carriers of X-linked CGD have some degree of risk for autoimmune or inflammatory complications (see "Symptoms" below) and are sometimes at a risk of infections too, so there may be benefits to testing.

There is no specific age that is "best" to pursue carrier testing: while X-linked carriers often report that they appreciate learning their carrier status early on – usually as a pre-teen or teenager – it is important that testing not be pursued until the child is sufficiently mature to understand and manage the implications of a positive test result. Prior to making the testing decision, parents may wish to consult a genetic counselor to discuss the logistics and the impact that a positive test result could have on their daughter's life, given her age, level of maturity and life circumstances.

Self-Advocacy

CGD affects about 1 in 200,000 people in the United States, with about 20 new cases diagnosed each year. Given the rarity of the disease, female carriers of X-linked CGD often have to advocate for themselves and/or for their affected children.

Since CGD is predominantly an X-linked disease, it was traditionally considered a male-only disease. Boys and men were thought to be affected by CGD while women with the defective gene were considered to be asymptomatic carriers. Today, it is known that some female "carriers" do experience physical symptoms--sometimes as severe as those experienced by males. Still, females with CGD often relay that medical providers dismiss their complaints as being psychosomatic in nature. Indeed, it can be difficult for symptomatic CGD carriers to convince doctors that they actually do have pain and physical symptoms related to CGD and to find competent treatment for those symptoms.

It is vital for CGD carriers to advocate for themselves to ensure they are receiving the best care. They may wish to seek out doctors and specialists who are known to be experts in CGD and recommended by other members of the CGD community or advocacy groups like the CGD Association of America. Before appointments, it is important for carriers to prepare themselves with the latest research findings, particularly when it comes to potential treatment options and clinical trials. They should also make a list of questions for the medical provider, so they make sure all of their concerns are addressed. During appointments, they should be open and honest about symptoms they may be experiencing and the treatment options they wish to explore.

Some carriers derive a great deal of satisfaction from joining CGD or X-linked carrier advocacy groups, or serving as an advocate for the CGD community as a whole. Connecting with other patient organizations, female carriers, and CGD patients on social media may prove to be a great way for carriers to connect with others in similar situations and to share their story to raise awareness for CGD.

Symptoms

Historically, many female carriers of X-linked CGD have struggled with challenging health issues without being aware of their CGD carrier status and how it can be related to these symptoms. We are still learning what environmental and personal features contribute to these health issues. These challenges, arising from compromised inflammatory and autoimmune responses, relate to the proportion of their functioning neutrophils, known as "lyonization." Lyonization results in a certain percentage of the carrier's neutrophils not producing enough NADPH-oxidase, an enzyme that engulfs and kills pathogens.

Inflammatory and autoimmune manifestations of carrying the gene for CGD may include:

- Increased risk of infection with certain bacteria or fungi (yeasts and molds)
- Cutaneous or lupus-like symptoms, such as:
  - skin infections and skin rashes
  - joint pain
  - chronic fatigue
  - photosensitivity
- Acne and boils
- Aphthous ulcer / canker sores
- Gastrointestinal symptoms
- Slower wound healing
- Chorioretinitis (inflammation of the choroid, the thin pigmented vascular coat of the eyes, and retina of the eye)
- Raynaud's syndrome (fingers, toes, ears, and tip of nose feel numb and cool in response to cold temperatures; often accompanied by changes in the color of the skin)
- High levels of anxiety and depression

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Diagnosing CGD Carrier Status

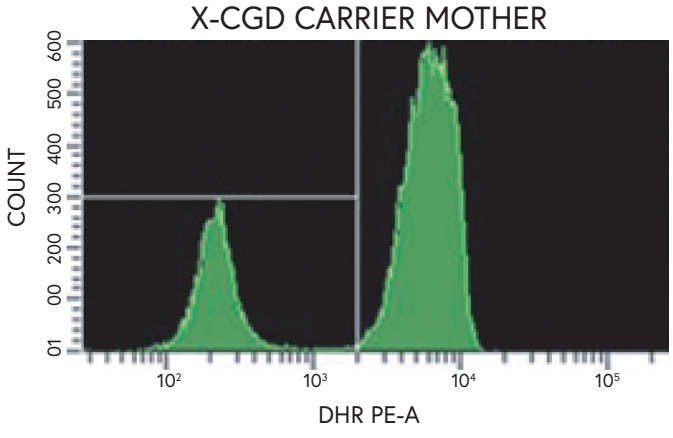
CGD carriers are usually diagnosed when a son, brother, or other male relative is diagnosed with CGD. If there is a family history of CGD and a female patient is showing symptoms, doctors should test for this condition.

Further, according to the recent study, "X-linked carriers of chronic granulomatous disease: Illness, lyonization, and stability" in the Journal of Clinical Immunology in 2018, low NADPH-oxidase activity percentage not only strongly predicts infection risk in carriers of X-linked CGD,, the carrier state itself is associated with inflammation and autoimmunity. Therefore, once carrier status is confirmed, other referrals to specialists may be recommended. The study also found that carriers of X-linked CGD with below 20 percent functioning neutrophil or positive DHR percentage (per the Dihydrorhodamine test below) experience more infection and may require CGD prophylaxis. It is important to note that a carrier's positive DHR percentage can change in a patient's lifetime, and the test may need to be ordered more than once, especially if carriers start developing more symptoms.

As a first step, the two tests to determine CGD carrier status are:

- Dihydrorhodamine (DHR) test can determine NADPH-oxidase activity or positive DHR percentage and can be performed on a very small sample of blood using a flow cytometer to measure the production of oxidants by individual blood neutrophils.
- Nitroblue tetrazolium (NBT) test can determine NADPH-oxidase activity. The DHR test has mostly replaced this test.

Typical two peak DHR pattern in following PMA activation of neutrophils from a female carrier of X-linked CGD.



Treatments

While each carrier of X-linked CGD is different due to her level of lyonization and other unrelated health or environmental issues, it is recommended that carriers be proactive about their health and seek out suitably qualified specialists/physicians who can prescribe appropriate treatments and guidance if they are experiencing symptoms. To find providers who are knowledgeable about CGD, please reach out to the CGDAA for referrals in your area. However, given the rarity of CGD, carriers often find they need to be proactive and seek out the following types of specialists, especially if they are experiencing symptoms:

- *Immunologist or hematologist:* These specialists can order a DHR test to determine X-Linked CGD carrier status. Depending on a carrier's positive DHR percentage, it may be important to be treated as a patient with CGD and to be prescribed some form of CGD prophylaxis, typically a daily antibiotic medication, such as trimethoprim-sulfamethoxazole (combination), also known as Bactrim(R)
    - CGD prophylaxis for patients with CGD includes antibiotic and antifungal medications to treat and prevent infection. Corticosteroids may be used to shrink granulomas (areas of inflamed tissue). CGD prophylaxis may also include interferon gamma-1b.
    - In addition, providers should encourage carriers to schedule regular follow-up appointments to monitor for infection and to be proactive about their health by booking appointments when symptoms of infection first arise.
- *Rheumatologist and/or Neurologist:* for lupus-like symptoms, such as skin rashes, chronic fatigue, joint and back issues
- *Gastroenterologist:* for symptoms of inflammatory bowel disease, such as abdominal pain and continuous diarrhea and bloody diarrhea
- *Dermatologist:* to assess skin/cystic acne and prescribe oral antibiotics or treatment with Accutane in severe cases
    - To protect skin from photosensitivity, reapply sunscreen regularly and limit sun exposure
- *Psychiatrist/Mental Health Therapist:* to assess for anxiety and depression and prescribe appropriate treatment and therapy
- *Sleep Specialist:* to assess sleeping patterns and determine if intervention is needed
- *Nutritionist:* to evaluate diet and consider healthy/anti-inflammatory options to reinforce self-care

> CGD can feel like an isolating disease, but remember you are not alone and have a community behind you.

Mental health

According to a recent study, "Health-Related Quality of Life and Emotional Health in X-linked Carriers of CGD in the UK," published in The Journal of Clinical Immunology in 2019, there are many factors that may impact the psychological health of CGD carriers, including being a caregiver for a child with chronic illness, genetic guilt, the presence of anxiety and depressive symptoms, and potential ill health of the subject themselves.

In the study, more than 40 percent of those X-linked carriers surveyed experienced moderate or greater levels of anxiety. Higher anxiety scores significantly correlated with higher depression scores and lower self-esteem, and higher levels of fatigue. Given that X-linked carriers often report higher levels of fatigue/chronic fatigue, medical providers should rule out low blood pressure or other underlying diseases.

Interestingly, the study found no correlation with the age of participant or degree of oxidative function. In other words, carriers who are not highly lyonized could still be affected and potentially have a poorer quality of life. Therefore, it is important for carriers to understand that simply carrying the genetic mutation for CGD can affect their mental health and seeing a psychiatrist or mental health professional could be considered part of an X-linked carrier's overall health care plan. Given these data points and numerous personal anecdotes from our members, the CGDAA has worked to reduce the stigma associated with asking for professional help for anxiety and depression.

"A Guide for Carriers of X-Linked Chronic Granulomatous Disease" was reviewed by the CGD Association of America Medical Advisory Board, the CGD Association of America X-linked Patient Advisory Board, Remember the Girls Medical Advisory Board, and the CGD Society.

Thank you to Horizon for supporting this educational program.

Felicia Morton
Executive Director, CGDAA

I founded the CGD Association of America (CGDAA) because I remember how it felt to receive my son's devastating CGD diagnosis in 2012. Once I recovered from the shock, I sought out mothers of sons who had CGD, and I was grateful to find a community of strong, knowledgeable women who helped me navigate the path ahead for my infant son. Soon, I learned that many of the "CGD Moms" I met were carriers of X-linked CGD, and they experienced health issues and ailments of their own. When I found out that I too was a CGD carrier, I felt empowered to make a difference. As a CGD advocate, it became clear to me that we needed to focus on the women and girls in our community too. With this in mind, the CGDAA came to fruition. From the beginning, we have been committed to raising awareness for CGD and advancing research for both male patients and female carriers. Knowing first-hand how isolating a rare disease can be, we also endeavor to create opportunities where CGD carriers can connect, learn, and support one another as we care for our families and ourselves.

Taylor Kane
Founder and Executive Director, Remember The Girls

I have spent most of my life as a rare disease advocate. I am the founder and executive director of Remember The Girls, an international non-profit organization that unites, educates and empowers female carriers of x-linked genetic disorders. My activism began when I was in grade school, shortly after my father died from the rare x-linked disorder Adrenoleukodystrophy (ALD) and I learned that I am a carrier of this devastating disease. I am an award-winning activist, an accomplished speaker, and a respected author, having recently published a memoir, *Rare Like Us: From Losing My Dad to Finding Myself in a Family Plagued by Genetic Disease*.

About The CGD Association of America (CGDAA)

CGD can feel like an isolating disease, but remember you are not alone and have a community behind you. The CGD Association of America (CGDAA) is committed to advocating for carriers of X-linked CGD by providing the latest news and research about carrier health issues and supporting research. Our goal is to provide educational materials to empower carriers of X-linked CGD to secure the medical care and treatment they need to live their best life. To support our mission, the CGDAA also organizes opportunities to connect with other carriers, share stories, and feel supported in an inclusive environment. The CGDAA is also available to connect you with our network of CGD specialists and helpful primary immunodeficiency resources.

For more information about CGD and X-linked CGD carriers, please visit the CGD Association of America website at www.cgdaa.org. We would also be happy to put you in touch with members of our CGDAA Medical Advisory Board for additional guidance.

Connect with us!

- Visit the CGDAA website at cgdaa.org
- Join our email newsletter
- Check out the CGDAA blog
- Follow us on Facebook, Instagram, and Twitter
- Email us at: info@cgdaa.org

Remember The Girls

To connect with carriers of CGD and other X-linked genetic diseases, please also consider joining the Remember The Girls Facebook support group: www.facebook.com/groups/rtgclosed. Remember The Girls is a non-profit organization dedicated to supporting and advocating for female carriers of X-linked disorders.

References and Additional Resources

"Health-Related Quality of Life and Emotional Health in X-Lined Carriers of Chronic Granulomatous Disease in the United Kingdom" Journal of Clinical Immunology

"Diagnosing Lupus" Lupus Foundation of America

"Skin Issues and Infections in Patients with CGD" Living With CGD

"What Medicines Treat Chronic Fatigue Syndrome?" WebMD

"A Guide for Female Carriers of X-linked CGD" CGD Society

"X-linked carriers of chronic granulomatous disease: Illness, lyonization, and Stability" Journal of Clinical Immunology

Chronic Granulomatous Disease: Epidemiology, Pathophysiology, and Genetic Basis of Disease Journal of the Pediatric Infectious Diseases Society

"X-Linked CGD Carriers, Long Overlooked, Are Getting More Attention" Immune Deficiency Foundation