CGDSociety

Supporting families affected by chronic granulomatous disorder

A guide for **female carriers of X-linked CGD**

About chronic granulomatous disorder

Chronic granulomatous disorder (CGD) prevents the immune system from fighting off certain infections. People with CGD carry a faulty gene, which means that some white blood cells, called phagocytes, don't work properly. As a result, people affected by CGD tend to get frequent bacterial and fungal infections, and need to take daily medication to stay healthy. Even if they take this medication, problems can still arise, leading to serious illnesses and prolonged periods in hospital.

CGD affects around six to eleven people in a million depending on the part of the world you live in.

Inheritance of CGD and being a carrier

CGD is an inherited genetic disorder, meaning it can be passed from one generation to the next. There are two ways children can inherit CGD from their parents. One way is called 'autosomal recessive' inheritance and the other way is 'X-linked' (sex-linked).

Autosomal recessive CGD develops because two copies of an abnormal gene have been inherited, one from each parent. Both males and females can have this type of CGD. To date there has been no evidence of health complications arising in carriers of the autosomal recessive form of CGD.

X-linked CGD (XL-CGD) affects males only. It is passed down from the mother to her son as a result of her carrying a genetic fault on her X chromosome. Only females can be X-linked carriers of CGD and they are usually identified because a male member of their family (father, son, brother, cousin, nephew) has been diagnosed with CGD.

Being a carrier of XL-CGD may have family planning implications for women and any carrier daughters they might have because the faulty X chromosome may be passed on. For each pregnancy there is a one in two chance that a son will be affected by CGD and a one in two chance that a daughter will be an XL-CGD carrier.

It is worth remembering that a man who has XL-CGD will also pass his faulty CGD gene on to all his daughters, making them all carriers. However, the defect won't be passed on to any sons.

Table 1. Summary of the differences between autosomal and XL-CGD

Mode of inheritance	Gender affected	Location of the faulty gene	Inheritance pattern	Health problems
Autosomal CGD	CGD affects both males and females	Faulty gene not present on a sex chromosome	Involves inheritance of copies of the abnormal gene from both a mother and father	Health problems in carriers of autosomal CGD have not been reported
XL-CGD	CGD affects males only	Faulty gene present on the 'X' sex chromosome	Abnormal gene is passed from mother to son	Carriers of XL-CGD have been shown to have associated health problems

Testing for being an XL-CGD carrier

The tests used for confirming you are a carrier of XL-CGD are the same as those used for diagnosing CGD and use a sample of your blood. They include the nitroblue tetrazolium test (NBT) and the dihydrorhodamine test (DHR). If the mutation causing CGD in your family is known, genetic analysis can be used to check for carrier status. The NBT and DHR test results for an XL-CGD carrier classically show a mixture of normal and abnormal white blood cells: some cells that are capable of producing chemicals that can kill bacteria and other cells that are not.

The proportion of affected and unaffected cells may differ from one XL-CGD carrier to another and may change over time. This and the health implications for individual carriers are the subject of ongoing research but the consensus is that periodic carrier retesting may be needed.

Testing and informing daughters of their carrier status

In the UK, daughters will be tested if they are older than 16 years of age with their consent or at a younger age if they have significant symptoms. If a daughter is found to be a tissue-type match and is being considered as a stem cell donor for a haematopoietic stem cell transplant (BMT) for an affected sibling, then their carrier status will be determined.

Clearly, having a daughter identified as an XL-CGD carrier will have implications for when she wants to start a family of her own. You should discuss with your health team when and how to approach discussing the test results with your daughter.

Coping with the news of being an XL-CGD carrier

Being told you are an XL-CGD carrier may have come as a complete shock to you and you may still be coming to terms with the news. A new diagnosis – especially one in which you are concerned may affect any children you've got or ones you might have in the future – can be daunting and worrying. Remember, being a carrier of CGD isn't down to anything that you did or did not do. It is not your fault or that of anyone else. Genetic conditions just happen.

Studies have shown that XL-CGD carriers have higher anxiety levels than the general population and higher levels than those seen in parents of other conditions. The reasons for feeling anxious may be to do with being tested yourself, getting your children tested or having to talk about the condition. There may be anger towards family members if CGD is not talked about as a matter that affects your family. The emotional effects may lead to feelings of sadness or depression. This is normal but if such feelings impact badly on your ability to function on a day-to-day basis, you should seek help. Be aware of the warning signs of stress, tension, anxiety and depression, and recognise when and how they are impacting on your life. Key symptoms to look out for are poor sleep and concentration, irritability and loss of enjoyment in things.

Once you have identified you have a problem, you can start to develop ways to counteract and cope with your feelings. This may be by distracting yourself by having 'me' time to do something new or something you enjoy. Relaxation and meditation techniques may also help reduce feelings of anger and anxiety. Other self-help approaches include the online resource Mood Gym.

If the impact on your daily life and well-being is severe, make sure your GP knows how you are feeling. Your GP may be able to refer you for counselling or to a clinical psychologist.

Remember, you don't have to feel like you're facing this alone. The CGD Society is here to provide you with information, help and support should you need it.

XL-CGD carrier health issues

In general, XL-CGD carrier females are healthy. However, some women may develop associated health problems, and in extreme cases the symptoms can be as severe as those experienced by people with CGD. Through research, more is being learned about the health implications of being an XL-CGD carrier.

The largest study of its kind, involving 81 XL-CGD carriers, identified a number of associated health issues with many carriers reporting one or more health problems.

These included:

Infections, including recurrent abscesses

Infections: 23% of XL-CGD carriers who participated in the study had a history of significant infections, with 17% having recurrent abscesses.

Inflammation involving the skin and gut and, less frequently, the respiratory system

Skin complications: 71% of XL-CGD carriers were highly sensitive to the sun (photosensitive), 40% had the lupus facial butterfly rash (Malar rash) and 10% had adult acne

Gut (gastrointestinal) problems: 34% had abdominal pain, 30% had diarrhoea, 20% had rectal bleeding, 10% had constipation and 9% had other gut problems

Respiratory complications: These were less commonly reported as a symptom, although 12% reported having asthma.

Autoimmune complications, including joint pain, ulcers and lupus

Joint pain and symptoms: 61% of XL-CGD carriers had joint pain (arthritis)

Mouth ulcers: 75% suffered from mouth ulcers, also known as apthous ulcers or canker sores

Symptoms associated with lupus: 32% had associated symptoms.

Excessive fatigue

Fatigue: Over half of the people studied reported, unprompted, excessive fatigue. This result was validated using the measurement tool Multidimensional Fatigue Symptom Inventory (MFSI).

Lupus and its link to XL-CGD carriers

Lupus erythematosus is an autoimmune disease caused by a fault in the way the body's immune system works. This means that in patients with lupus the immune system gets confused and attacks the body's own healthy tissues, in much the same way as it would attack an infection, causing inflammation in various parts of the body, e.g. the skin and kidneys.

There are two forms of lupus:

- Discoid lupus erythematosus (DLE), which is largely confined to the skin
- Systemic lupus erythematosus (SLE), which affects the body's other tissues.

The common features of lupus are skin rashes and joint pains. Symptoms of SLE may include inflammation of internal organs, such as the lungs, heart, nervous system and kidneys.

There are a number of XL-CGD carrier females who have 'lupus-like' symptoms – mainly skin rashes that are very sensitive to the sun, joint pain and tiredness. Doctors refer to these symptoms as 'lupus-like' because most XL-CGD carrier females who have been tested for lupus do not have the auto-antibodies used to diagnose lupus or, if they do, their blood test results are only weakly positive.

Lupus is diagnosed by the symptoms people have and blood tests. These blood tests look for particular types of auto-antibodies that interfere in the way cells work in the body. One of the most common tests looks for anti-nuclear antibodies (ANA), and antibodies to double-stranded DNA (which makes up genes and chromosomes). However, these tests can show as negative in some people who do actually have lupus, especially DLE. This seems to be particularly true of XL-CGD carriers.

For many people, lupus-like symptoms are no more than a nuisance. Others who have troublesome symptoms may benefit from the treatments used in lupus, even if their lupus blood tests are negative. SLE can be a more unpredictable condition and should be carefully monitored by a rheumatologist (often in a special lupus clinic).

What symptoms of lupus should I look out for?

Symptoms to look out for are skin rashes that develop on parts of the body which are exposed to the sun, such as the face, wrists, hands and chest. Some people find that they have problems with their hands in the cold, with their skin becoming very white or blue in colour. This is a very common condition and is known as Raynaud's phenomenon. Many XL-CGD carriers have problems with their joints, mostly involving pain and some swelling. Lupus-like symptoms are often associated with feeling very tired. If you experience any lupus-like symptoms it is best to get yourself checked out by your doctor.

If you are an XL-CGD carrier and think you may have lupus-like symptoms, consult your GP. Your GP may refer you for screening tests and an assessment by a rheumatologist. Lupus-like symptoms need to be treated seriously. If they're significant, you should be referred to a rheumatologist or dermatologist and given appropriate treatment. It is important that your GP (or rheumatologist) understands that there is a known link between lupus-like problems and being a carrier of CGD. If you have any concerns, discuss them with your physician and health team.

Dealing with symptoms

Health complications associated with being an XL-CGD carrier need to be taken seriously and reported to your GP.

Infections

Doctors may prescribe prophylactic antibiotics to prevent and treat infections.

Mouth ulcers

Mouth ulcers can be treated but may keep coming back. Recommendations for preventing and dealing with mouth ulcers are as follows:

- Maintain good dental hygiene and use a mouthwash. The best way to avoid mouth ulcers is by cleaning your teeth twice a day and using an alcohol-free, anti-bacterial mouthwash containing chlorohexideine, such as Corsodyl. (Please be aware that using Corsodyl over a long period of time can cause teeth to discolour and the tongue to feel too sensitive, so you may need to stop using it for a while, then restart.)

- When you develop an ulcer, continue to clean your teeth and mouth, even if it is painful. Again, use an alcohol-free, anti-bacterial mouthwash containing chlorohexideine, such as Corsodyl. Another recommended solution is Orobase, a thick paste that protects the ulcers and allows them to heal. You must always check with your nurse or doctor before using Orobase, as it contains a mild steroid (Adcortyl).

- Your doctor may prescribe other medication that contains a steroid as it is the most effective remedy for difficult-to-treat mouth ulcers. The steroid helps ulcers heal quicker although it doesn't stop new ones occurring. Steroid treatments include:

  – Hydrocortisone hemisuccinate pellets (Corlan), 2.5 mg used four times daily – you put the pellet next to or on the ulcer.

  – Betamethasone, 500 mg soluble tablets dissolved in 15 ml of water to make a mouth rinse, used four times daily for a few minutes. This can be a very useful approach if there are many ulcers in the mouth.

- If the ulcers are painful, you can use a sore mouth gel, such as Bonjela, or the chemist's own brand equivalent. Some gels are not suitable for children, so make sure you read the instruction leaflet carefully. Alternatively, you can try Difflam mouth spray as a local anaesthetic, or take painkillers.

- When the ulcers just won't go away, talk to your doctor or specialist nurse if you're concerned. There may be an underlying, ongoing minor infection causing them that may need treating with antibiotics.

Topical tetracyclines may reduce the severity of ulceration, e.g. Doxycycline, 100 mg in 10 ml of water used as a month rinse four times daily. This treatment is only used for people older than 12 years of age.

Sun sensitivity

Being extra-sensitive to the sun means you may burn more easily or get skin rashes or blisters. Our sun safety tips include:

- Wear a high factor sun cream (SPF 30 upwards) or sun block. Reapply it every couple of hours.
- Wear a hat, sunglasses and T-shirt.
- The sun can get through clothes, so wear clothes with a 'sun protection factor' (SPF), or dark clothes (which protect the skin more than lighter ones).
- Put sun cream on your hands, feet, face, ears and neck – common places to miss!
- Avoid the sun when it is at its strongest – between 12 noon and 3pm.
- The sun reflects off water, making it more intense. Be particularly careful if you are swimming or on a boat trip.
- Moisturise your skin when you've been in the sun.
- Drink plenty of water to stop dehydration.

Lupus-like symptoms

People who have skin rashes and joint pain are usually treated with creams (often containing some steroids) or anti-inflammatory medicines. Some people find that anti-malarial drugs, such as Hydroxychloroquine, are also effective in treating the symptoms of lupus, particularly in preventing severe recurrent mouth ulcers and sun-sensitive skin rashes, and possibly in reducing the feelings of tiredness, but a doctor must prescribe these specifically for you.

People who have more serious complications associated with systemic lupus may be treated with steroid tablets or other drugs known as immunosuppressants, which alleviate symptoms by damping down the immune system. When these medicines are prescribed, your doctor will want to review your health regularly through blood tests and regular check-ups.

Skin rashes associated with lupus are often very sensitive to the sun. It's best to avoid sunbathing and to wear a high factor sun cream (SPF 30 or higher) when outside (this may be available on prescription from your GP). In cold weather, people who have problems with Raynaud's phenomenon should keep warm and wear thick gloves and socks or tights.

Fatigue

Tiredness tends to come and go, so it's best to try and get some rest when you are not feeling good and make the most of days when you are.

There might be many reasons for the excessive fatigue seen in XL-CGD carriers. Some of the reasons may include caring for a child with a chronic illness, the effect of any chronic inflammation on the body and dealing with any emotional problems associated with being an XL-CGD carrier.

Family planning

XL-CGD carrier women can become pregnant, have babies and may not experience any adverse effects to their health. For each pregnancy there is a one in two chance that a son will inherit CGD and a one in two chance that a daughter will be an XL-CGD carrier. If your male partner has XL-CGD, then all your daughters will be carriers but your sons will not be affected by CGD or be a carrier of the condition.

Before getting pregnant

If you are an XL-CGD carrier it is worth discussing with your doctor your plans for starting a family. Your doctor may refer you to a hospital genetic counselling service that will offer valuable guidance and advice on family planning issues. If this is not possible, you should inform your doctor as soon as you know you are pregnant.

If you are affected by any health problems associated with being an XL-CGD carrier or taking medication to relieve symptoms, your doctor will take these into account in the management of your pregnancy. Pregnancy can alleviate or worsen problems for many conditions, and any adverse health issues will be carefully monitored as your pregnancy progresses.

There are options available to determine if you are carrying a child affected by CGD. These include:

- **Prenatal testing** during early pregnancy using tissue (chorionic villus sampling, or CVS) or fluid (amniocentesis) from the womb.

- **Free fetal DNA testing** during the first nine weeks of pregnancy. This determines the sex of the baby and only a sample of the mother's blood is needed. Some hospitals may offer this to carriers of XL-CGD. In the UK, the family clinic at Great Ormond Street Hospital in London can offer this service to families.

The technique of preimplantation genetic diagnosis involves IVF (in vitro fertilisation) treatment and makes it possible to see whether an embryo has CGD or not before it is placed back in the womb.

Research and XL-CGD carriers

Research into the possible health complications of being a carrier of XL-CGD is still in its infancy. The CGD Society is working hard to raise awareness of health problems experienced by people who are carriers of XL-CGD and to encourage more research in this area.

You may find the following research papers that examine the health of XL-CGD carriers of interest.

'Health-related quality of life and emotional health in X-linked carriers of chronic granulomatous disease in the United Kingdom'. Battersby AC, Braggins H, Pearce MS, McKendrick F, Campbell M, Burns S, Cale CM, Goldblatt D, Gennery AR. *Journal of Clinical Immunology*, 2019 Feb; 39(2): 195–199.

The results found that over 40 per cent of the 61 XL-CGD carriers surveyed had experienced moderate or greater levels of anxiety, with only a third having levels equivalent to those of the general population. The high

anxiety scores were strongly associated with high levels of depression, low self-esteem, the presence of joint or bowel symptoms and higher levels of fatigue. Significantly, XL-CGD carriers were found to have lower quality of life scores than CGD patients in the domains of vitality, emotional well-being and mental health.

'X-linked carriers of chronic granulomatous disease: illness, lyonization, and stability'. Marciano BE, Zerbe CS, Falcone EL, Ding L, DeRavin SS, Daub J, Kreuzburg S, Yockey L, Hunsberger S, Foruraghi L, Barnhart LA, Matharu K, Anderson V, Darnell DN, Frein C, Fink DL, Lau KP, Long Priel DA, Gallin JI, Malech HL, Uzel G, Freeman AF, Kuhns DB, Rosenzweig SD, Holland SM. *Journal of Allergy and Clinical Immunology*, 2018 Jan; 141(1): 365–371.

'Inflammatory and autoimmune manifestations in X-linked carriers of chronic granulomatous disease in the United Kingdom'. Battersby AC, Braggins H, Pearce MS, Cale CM, Burns SO, Hackett S, Hughes S, Barge D, Goldblatt D, Gennery AR. *Journal of Allergy and Clinical Immunology*, 2017 Aug; 140(2): 628–630.

The two studies above showed that some XL-CGD carriers have similar problems with infection, inflammation and autoimmunity as seen in people with CGD. The studies underline the recommendation that the health of symptomatic XL-CGD carriers should be managed proactively and reviewed by suitably qualified specialist doctors.

'Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease'. Battersby AC, Cale CM, Goldblatt D, Gennery AR. *Journal of Clinical Immunology*, 2013 Nov; 33(8): 1276–84.

This is a review examining the literature about clinical manifestations of disease in XL-CGD carriers.

'Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology'. Cale CM, Morton L, Goldblatt D. *Clinical and Experimental Immunology*, 2007 Apr; 148(1): 79–84.

This research found that symptoms of photosensitivity, skin rashes, joint pains, fatigue and mouth ulcers are common in XL-CGD carriers. It recommends that symptoms should be taken seriously and GPs consider referring patients to a rheumatologist or dermatologist so appropriate treatment can begin. It's likely that tests for lupus will be negative but this should not influence diagnosis and treatment of people who have 'lupus-like' symptoms.

'Abnormal apoptosis in chronic granulomatous disease and autoantibody production characteristic of lupus'. Sanford AN, Suriano AR, Herche D, Dietzmann K, Sullivan KE. *Rheumatology* (Oxford). 2006 Feb; 45(2): 178–81.

This study found a link between developing lupus and the inability of XL-CGD carriers' white blood cells to die and be cleared away by other cells in a normal, coordinated way.

'Lupus erythematosus tumidus and chronic discoid lupus erythematosus in carriers of X-linked chronic granulomatous disease'. Rupec RA, Petropoulou T, Belohradsky BH, Walchner M, Liese JG, Plewing G, Messer G. *European Journal of Dermatology*, 2000 Apr–May; 10(3): 184–9.

The report describes two XL-CGD carriers who developed discoid lupus erythematosus (DLE) and a photosensitive type of lupus called lupus erythematosus tumidus.

'Chronic granulomatous disease: a case study of a symptomatic carrier'. Romera Modamio G, Martín Mateos MA, González Enseñat MA, Pastor Gómez MA. *Journal of Investigational Allergology and Clinical Immunology*, 1997 Jan–Feb; 7(1): 57–61.

This paper showed how XL-CGD carriers may sometimes have symptoms of the condition themselves.

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About the CGD Society

The Chronic Granulomatous Disorder Society (CGD Society) is the leading global charity dedicated to promoting an understanding of CGD and providing support to affected individuals and their families.

Our website **https://cgdsociety.org** provides medical information and practical advice on living with CGD. It is free to become a member of the CGD Society. Please go to **https://cgdsociety.org/home/become-a-member**.

If we can be of any help, please contact us at **hello@cgdsociety.org** or on **0800 987 8988**, where you can leave a message.

Our charity is reliant on voluntary donations. To make a donation, please go to **https://cgdsociety.org/home/donate-now**.