SCID

Severe combined immunodeficiency (SCID)

www.immunodeficiencyuk.org
hello@immunodeficiencyuk.org
0800 987 8986

Great Ormond Street Hospital for Children NHS Foundation Trust

THE great north CHILDREN'S HOSPITAL

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this booklet

This booklet has been produced jointly between Immunodeficiency UK, Great Ormond Street Hospital (GOSH) and the Great North Children's Hospital. The information has been reviewed by the Immunodeficiency UK Medical Advisory Panel and Patient Representative Panel and by families affected by PID. It is designed to help answer the questions families may have about the immune condition called severe combined immunodeficiency (SCID) but should not replace advice from a clinical immunologist.

Contents

Severe combined immunodeficiency (SCID)
First edition April 2017

Published by Immunodeficiency UK (www.immunodeficiencyuk.org)

What is severe combined immunodeficiency (SCID)?

Severe combined immunodeficiency (SCID) is the name given to a group of rare, inherited disorders that cause major abnormalities of the immune system. They form part of a larger group of conditions known as primary immunodeficiencies. The immune system abnormalities in SCID lead to greatly increased risks of infection and other complications that are life-threatening. Affected infants become unwell within the first few months of life, and before modern medication and treatments were available, most affected babies did not survive beyond their first year. Today, doctors understand much more about SCID. Treatment is now available that can reduce the risk of serious infection, and in many cases, cure the disorder.

There are many different types of SCID, each with different genetic causes. However, infants affected by the various types of SCID have many features in common and these are described in this leaflet. In all infants affected by SCID, specialised white blood cells, known as lymphocytes, are missing or not functioning properly. The three main types of lymphocytes that can be affected are called T-cells, B-cells and natural killer ('NK') cells.

What causes it?

SCID is an inherited condition, meaning it is passed on in families in the same way as physical characteristics, such as eye colour, are passed from parent to child. It is caused by a mistake (or mutation) in a child's genetic make-up. Specialists in genetics and genetic counselling are on hand to talk through the inheritance of SCID with you if needed, and we have a separate information leaflet devoted to the genetics of primary immunodeficiency available on our website.

In infants affected by SCID, a genetic mistake results in the absence or malfunction of a protein that is necessary for normal development and/or function of the immune system. Many different genes can be affected, each causing a different type of SCID. Recent developments in genetics mean that doctors are now often able to make a specific SCID diagnosis. The names given to the different types of SCID are based on the particular protein or gene that is affected. Some of the more frequently encountered types include common gamma chain deficiency, adenosine deaminase (ADA) deficiency, JAK 3 kinase deficiency, MHC class II deficiency, and recombinase activating gene (RAG) deficiency. Although the management and treatment of infants with SCID is usually very similar for all types, it is important to know the exact cause: (a) because in some conditions there may be specific treatments available, and (b) to allow accurate genetic counselling for future pregnancies.

What are the signs and symptoms of SCID?

Babies with SCID may seem well at birth and for the first few weeks of life. This is because they are partly protected by antibodies passed from mother to baby across the placenta during the last few months of pregnancy.

The first signs of SCID usually occur within the first three to six months. The baby is likely to suffer infections more frequently than other infants, and ordinary problems, such as coughs and colds, will seem more severe and last longer than would be expected, requiring repeated and prolonged courses of treatment. Thrush (an infection caused by the yeast candida) in the mouth and/or nappy area may be severe and persistent, not clearing with usual treatment. The infant may feed poorly, have chronic diarrhoea and fail to gain weight normally, even if no definite infection is found. Skin rashes are common, and may be caused by thrush, or sometimes by a reaction in the skin caused by maternal blood cells which have crossed the placenta at birth.

Germs in the environment that don't cause disease in healthy individuals can cause serious and life-threatening illness in a child with SCID. In particular, the fungi *Pneumocystis jirovecii* (PJP) and *Aspergillus*, and the virus cytomegalovirus (CMV), can cause severe infection (most frequently pneumonia). The parasite Cryptosporidium (sometimes found in drinking water) can cause severe diarrhoea and sometimes liver disease in children with SCID.

Common childhood infections, such as chickenpox (varicella) and cold sore virus (herpes simplex), can also be dangerous for a baby with SCID and may be life-threatening.

How is it diagnosed?

Before parents know their baby has SCID they may seek help from their family doctor (GP) or local A&E because of repeated infections, poor weight gain or feeding problems, and the baby may be referred to a local paediatrician. However, the first indication that something is wrong can be a serious infection that causes rapid deterioration in the baby's condition, requiring urgent admission to hospital, and sometimes to an intensive care unit. As a result of routine investigations, SCID may be suspected, usually because of a low lymphocyte count in the blood. As soon as the possibility of SCID is suspected, the infant will be referred to a specialist immunology centre, and further investigations are then necessary to confirm the diagnosis, and subsequently to determine the type of SCID.

How is it treated?

There are two specialist centres in the UK that treat children with SCID – Great Ormond Street Hospital (GOSH) in London, and the Great North Children's Hospital (GNCH) in Newcastle. Treatment will begin when the child is referred to one of these centres.

Great Ormond Street Hospital and the Great North Children's Hospital are specialist centres for children affected by SCID.

The immediate priorities will be to provide an environment which protects from infection, to perform appropriate tests and assessments, and to start treatment for infection and other protective measures. Subsequently, possible treatments that can correct the defect will be discussed. These include haematopoietic stem cell transplantation (HSCT, or SCT) and gene therapy. HSCT is the most usual treatment, while gene therapy is only suitable in a small number of specific conditions and is still undergoing clinical trials.

Starting treatment

Your child will be admitted to a room or an area with 'filtered air' (to remove germs). He or she will be confined to this room and will not be able to mix with other children or go to the ward playroom. You will be able to stay with your child and will be encouraged to continue to feed, care for and play with him or her as much as you want. Visitors will be kept to a minimum, and no one who has an infection will be allowed to visit. You will be told about the ways that you can avoid passing on infection, such as washing your hands thoroughly.

Further blood tests will be performed to confirm the diagnosis and type of SCID. More specialised tests will subsequently be carried out to determine the precise genetic abnormality. Other investigations will also be necessary to identify any undetected infection, including chest x-rays, scans and tests on samples of blood, urine, faeces and mucus from the throat.

Most children with SCID will have similar symptoms and will receive the same treatments whatever the type of SCID. In most cases a 'central line' (sometimes called a central venous catheter or Hickman® line) will be inserted. This is a silicone tube which is put into a large vein and fixed to the skin surface, usually on the chest. It requires a small operation under general anaesthetic, but it allows blood to be taken and intravenous medicine to be given without the need for any needles, and is sometimes also used to give intravenous nutrition.

Medication
Antibiotics, antiviral and antifungal medicines will be needed to protect against serious infection. Most medicines can be given in the form of syrups. If the baby has an active infection, it may be necessary to give the medicines into a vein, through a drip (or through the central venous catheter).

Immunoglobulin (antibody) therapy
Babies affected by SCID are not able to produce their own antibodies to fight infection. The missing antibodies are replaced by giving treatment with immunoglobulin.

Immunoglobulin is a solution of human antibodies which have been purified from normal blood donations. It provides temporary protection against infection and it is given either intravenously (into a vein) or subcutaneously (injection into the skin). Your child will receive regular immunoglobulin therapy from the time of diagnosis. As it is derived from donor blood, giving immunoglobulin carries a very small risk of transmitting infections. You will have the chance to discuss immunoglobulin therapy in more detail, and the method by which it will be given, with the immunologist or nurse specialist before treatment starts. Further information about immunoglobulin treatment can be found in a range of leaflets from Immunodeficiency UK.

Blood transfusions
It may be necessary to give blood, platelet or plasma transfusions. It is important that these treatments are given, but some precautions are needed. Specially prepared 'irradiated' blood is given. Irradiating donor blood preserves the red blood cells and platelets but removes any immune cells that could cause a bad reaction. The donor blood is also screened to ensure it does not contain CMV, which could cause problems for a child with SCID. Any blood, platelet or plasma transfusion will be labelled 'CMV negative' and 'Irradiated'.

CMV, breast feeding and nutrition
CMV is a very common virus in the general population, with approximately 50 to 80 per cent of adults in the UK testing positive for the virus. It is spread through bodily fluids, such as saliva, urine and breast milk. In most cases CMV does not cause any symptoms, but in some people flu-like symptoms, including a high temperature, sore throat and swollen glands, may occur. Once you have had CMV, the virus stays in your body but is inactive, and in a healthy person does not cause any further problems.

CMV can be serious for infants with SCID. If a mother is breastfeeding a child with SCID, a blood test will be taken from the mother to see if she is CMV positive because the virus can be transmitted in breast milk. While waiting for the result, mothers are supported to express their milk. The result normally comes back after 24 to 48 hours. If the result is positive, it is advised to stop breastfeeding, owing to the risk of transmitting CMV to the baby, and formula milk feeds will be recommended. If a baby with SCID is not thriving, extra calories, vitamins and minerals may be needed. These can be given in special drinks or medicines. If your baby is feeding poorly, extra feeds can be given through a nasogastric tube (a tube inserted into the stomach through the nose). However, in some cases it may be necessary to give feeding called TPN (total parenteral nutrition), in which all the nutrients and calories are given intravenously, directly into the bloodstream through a central venous catheter.

Vaccination
In many cases, some early infant vaccines will already have been given before the diagnosis of SCID is recognised. Most of these are completely safe and do not cause any problems because they are not live vaccines. However, it is important for live vaccines to be avoided in infants with SCID. These include live polio vaccine (no longer part of the routine immunisation schedule in the UK), BCG and measles/mumps/rubella (MMR). If your child or another family member has received live polio vaccine due to vaccination in another country, then the doctors should be made aware. Rotavirus vaccine, which has recently been added to the routine UK schedule, is given in the first few months of life, and is also a live vaccine. It may result in the vaccine strain of the virus persisting in the gut of infants with SCID. If your baby has received rotavirus vaccine, this will be tested as part of the initial set of investigations.

Once the diagnosis of SCID is established, no further routine vaccines are recommended until treatment has been completed. Regular immunoglobulin replacement treatment will provide protection against a large number of germs, including those covered by routine vaccines.

Other issues
Prolonged hospitalisation, separation from extended family, blood tests and uncomfortable procedures will contribute to a great deal of stress and anxiety and even guilt for parents of a child with SCID. Support is available from psychologists, social workers and patient support groups.

It may be possible for your child to go home for a period of time before he or she goes ahead with corrective treatment. In this situation the immunology team will contact local doctors and community nurses beforehand to make arrangements if treatments need to be given at home or in the local hospital.

Most parents are delighted to get home, but it can be a worrying time. Anxiety about catching or passing on an infection can make life very stressful. The hospital team, nurses and support groups will provide you with guidance on protecting your child from infection, keeping the house clean and coping with diet and medication. If you are worried at any time, you are always able to ring the hospital and speak to an immunologist or a nurse.

Definitive (potentially curative) treatment of SCID

Haematopoietic stem cell transplantation (HSCT)
Brief information is provided about HSCT here, but much more detailed information can be found in specific leaflets provided by the bone marrow transplant (BMT) unit.

In most cases, HSCT offers the only long-term cure for SCID. HSCT aims to replace the faulty immune system with an immune system from a healthy donor. Stem cells, from which all the cells of the immune system develop, can be obtained from healthy bone marrow (bone marrow transplantation; BMT), or in some cases, from umbilical cord blood or donor blood. Bone marrow, blood or umbilical cord blood can be taken from a suitable, healthy donor and given by transfusion into a vein to a child with SCID.

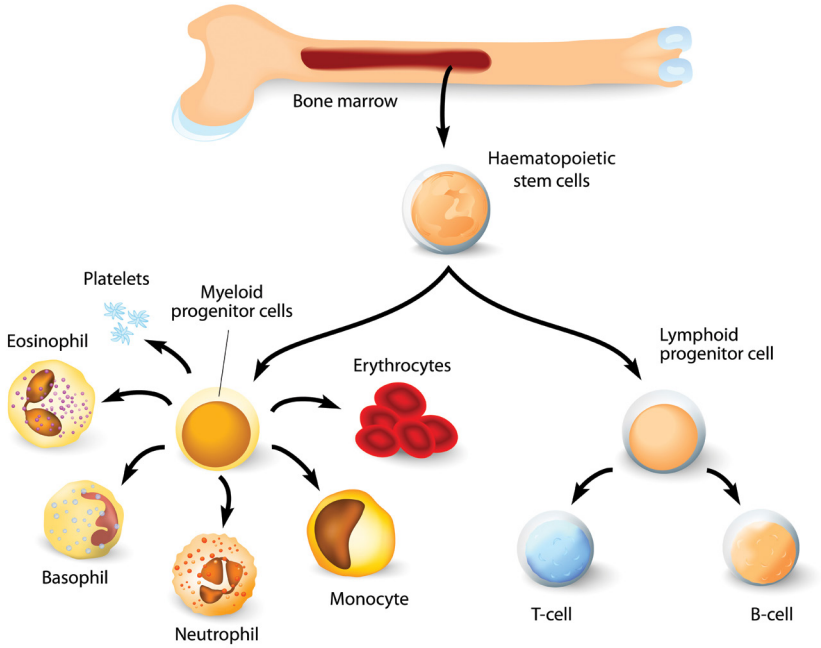
An HSCT is not an operation like a heart or kidney transplant. Stem cells contained in the donor bone marrow are able to find their way from the bloodstream to your child's bone marrow, where they start to produce healthy blood cells. An HSCT does involve a number of risks, and complications can arise afterwards – some of which are temporary, others of which can be life-threatening. You will have the opportunity to discuss this in detail with an immunologist and transplant consultant on several occasions.

Soon after the diagnosis of SCID is confirmed, blood samples will be collected from members of the family to determine the tissue type of each member. If a family member is found to have an identical tissue type to the affected baby, they will be selected to be the donor. There is a 1 in 4 (25 per cent) chance that full siblings will have identical tissue types. If there is no suitable family donor an unrelated donor will be sought from the worldwide donor registries.

Donating bone marrow involves having a general anaesthetic but it is a relatively minor procedure. Donating stem cells obtained from blood involves taking some preparatory medication (which is given by injection) and undergoing a procedure known as 'apheresis'. Both types of donation involve minimal risk to the donor.

Once a donor has been identified, the family will meet members of the transplant team, who will ensure that the family has ample opportunity to see the transplant unit, discuss worries and ask questions. In most cases, chemotherapy drugs are needed to prepare the body to receive a new immune system, reducing the chance of rejection of the new bone marrow by the child's own immune cells. If a perfectly matched bone marrow donor has been found within the immediate family, then chemotherapy is not always necessary. Not all children will receive exactly the same drug combinations.

How blood cells are made



Gene therapy
Gene therapy aims to correct the underlying genetic abnormality by replacing the faulty gene in immune cells with a normal copy. It is currently undergoing clinical trials in selected patients who have certain specific conditions. It has been successful in correcting the immune deficiency in a small number of children affected by X-linked SCID and the ADA-deficient form of SCID. It may also be available soon for some other genetic forms of SCID. For the child, gene therapy is a relatively straightforward procedure and if successful offers a cure.

Gene therapy involves taking stem cells from an affected child's blood or bone marrow. These are then manipulated in the laboratory, inserting a normal copy of the defective genes using complex technology. Once corrected, the cells are returned a few days later by transfusion into the child. As in a stem cell transplant, these new stem cells find their way to the bone marrow, where they start to produce healthy immune cells. This is known as somatic gene therapy – altered genetic material is only present in cells derived from the infused stem cells and cannot be passed on to future generations.

People worry about the idea of gene therapy because of the possibilities of eugenics (generating an improved population through selection of its best characteristics for breeding). Manipulating genes that can be passed on to offspring is known as germ line gene therapy and is not permitted by law.

Further information about gene therapy will be provided by the gene therapy team as needed.

What does this mean for the future?

Continuing developments and improvements are transforming the lives of children with SCID. Advances in diagnostic techniques and genetic technology, improved treatments and better medications enable many children with SCID to proceed through stem cell transplant safely. It is likely that gene therapy will continue to develop and become applicable to more types of SCID.

Genetic counselling
In many cases, the genetic mistake causing SCID can now be identified. This means that accurate genetic counselling is available for the immediate and extended family, and that prenatal diagnosis is possible for future pregnancies. Referral to local genetic counselling services can be arranged, and in some situations a joint counselling appointment with a genetics specialist and an immunologist can be helpful. More information about the genetic aspects of primary immunodeficiency can be found in a leaflet on this topic, which is available on our website.

Newborn screening for SCID
Unless there is a previous family history of SCID, most infants with SCID are only diagnosed after problems with serious infection occur. Early diagnosis of SCID has been shown to significantly improve survival (to over 90 per cent). This is because infants diagnosed soon after birth can be started on preventative medications and other measures taken to prevent serious infections from very early on. Much work is being undertaken towards introducing newborn screening for SCID worldwide, and several countries now have established screening programmes for SCID. This is not currently available in the UK. However, we continue to work closely with the UK National Screening Committee (UKNSC) and are hopeful that a national screening programme for SCID will be approved in the UK soon.

Further support and information

It can be helpful to meet another family who has a child with SCID and who has undergone HSCT or gene therapy. Speak to your immunology team, who may be able to arrange a meeting with a suitable family.

Information on how to join the bone marrow donor registry can be accessed from the Anthony Nolan charity by ringing 0303 303 3000 or visiting **www.anthonynolan.org**

Glossary of terms

adenosine deaminase (ADA) an enzyme found in lymphocytes (and other cells) responsible for removing certain toxins produced by their metabolism. Absence of ADA leads to failure of lymphocyte function and is one of the causes of severe combined immunodeficiency (SCID).

antigen any molecule that stimulates an immune response. Antigens include molecules that form part of foreign substances or infecting organisms, and also those carried on the body's own tissues.

apheresis a procedure in which the blood of a donor or patient is passed through a machine that separates out one particular part of the blood and returns the remainder to the patient's circulation. Apheresis is used to harvest peripheral blood stem cells from donors for stem cell transplantation.

B-cells (B-lymphocytes) cells of the immune system produced in the bone marrow and involved in the production of antibodies.

BCG a live vaccine against tuberculosis.

bone marrow soft, spongy tissue located in the hollow centres of most bones that contains developing blood cells and cells of the immune system.

bone marrow transplantation (BMT) transfer of bone marrow, obtained by aspiration usually from the hip bones, from a donor – either related or unrelated – to a recipient. The donor bone marrow replaces the recipient bone marrow, giving the recipient a new immune system and curing the immunodeficiency (See also Haematopoietic stem cell transplantation).

carrier an individual who carries the faulty gene for a specific condition without symptoms.

central venous catheter a thin silicone tube inserted under general anaesthetic into a large vein in the neck and tunnelled under the skin. It is used to administer medications, fluids and nutrition, and for taking blood samples. It can remain in place for many months but needs to be looked after carefully to prevent infection. It may be referred to by its brand name, for instance, Hickman® or Broviac™.

chemotherapy a type of treatment that uses medication to destroy cancer cells. In immunology, chemotherapy is used to destroy a person's immune cells in preparation for stem cell (or bone marrow) transplantation.

cytomegalovirus a virus that causes a mild illness in healthy individuals, but can cause severe and life-threatening disease in people with primary immune deficiency.

deficiency a lack of or shortage.

donor an individual who could donate bone marrow or stem cells for transplantation. Donors may be family members, or unrelated, but need to be well matched with the potential recipient by tissue-typing.

eugenics generating an improved population through selection of its best characteristics for breeding or eradication of unwanted characteristics.

fungus member of a class of relatively primitive microorganisms, including mushrooms, yeasts and moulds. Fungal infections can be particularly serious in people with primary immune deficiency.

gene section of DNA on a chromosome that codes for a functional RNA molecule and thus a protein. Put another way, a word rather than a letter in the genetic code. Genes are the fundamental units of inheritance that carry the instructions for how the body grows and develops.

gene therapy attempting to cure genetic diseases by placing a normal 'healthy' gene into cells that have a faulty version of that gene.

genetic counselling advice from a specialist geneticist regarding the implications of carrying or being affected by a genetic disorder.

geneticist an expert in the study of genes and heredity.

haematopoietic stem cell transplantation (HSCT) transfer of bone marrow (obtained by a medical procedure) or stem cells (obtained from blood or stored umbilical cord blood) from a donor – either related or unrelated – to a recipient. Haematopoietic means blood-forming. The donor cells are given by intravenous infusion and make their way to the recipient bone marrow to provide a new immune system, curing the immunodeficiency.

immune deficiency when the immune system's ability to fight infectious disease is compromised or entirely absent.

immune system the structures and processes that protect the body against infection and disease.

immunoglobulin replacement therapy administration of immunoglobulin purified from plasma to people with immune deficiency. The immunoglobulin contains antibodies that help protect against infection. This treatment can be given through a vein or under the skin.

immunoglobulins proteins (globulins) in the body that act as antibodies. They work to protect against and fight off infections. They are produced by specialist white blood cells (plasma cells/B-cells) and are present in blood serum and other body fluids. There are several different types (IgA, IgE, IgG and IgM), and these have different functions.

inheritance passing down of genetic information from parents to children.

intravenous inside or into a vein; for example, an immunoglobulin infusion may be given directly into a vein.

lymphocytes small white blood cells, normally present in the blood and in lymphoid tissue, that carry out specialised functions of the immune system. There are two major forms of lymphocytes, B-cells and T-cells, which have distinct but related functions in generating an immune response and are responsible for immunological 'memory'.

MMR vaccine a live vaccine against measles, mumps and rubella (German measles).

mutation a change in the structure of a gene or group of genes. Such changes can be passed on to the next generation. Many mutations cause no harm, but others can cause genetic disorders, such as primary immune deficiencies.

nasogastric tube a thin tube passed through the nose, down the oesophagus (or food pipe) into the stomach. It is used to deliver fluid and feed supplements directly into the stomach, by-passing the mouth and throat.

natural killer (NK) cells a type of lymphocyte particularly important in fighting virus infections and protecting against cancer.

newborn screening testing performed in the newborn period to screen for inherited conditions.

opportunistic infection an infection occurring in immunodeficient or immunosuppressed persons, caused by organisms that do not cause disease in people with normal immune systems.

plasma straw-coloured liquid part of the blood (that is, excluding blood cells) which consists of water containing a large number of dissolved substances including proteins, salts (especially sodium and potassium chlorides and bicarbonates), food material (glucose, amino acids, fats), hormones, vitamins and excretory materials.

platelets tiny cell fragments which circulate in the bloodstream and are important for preventing bleeding by forming blood clots.

Pneumocystis jirovecii pneumonia (PJP) an 'opportunistic' infection that does not usually cause illness except in people with defective immune systems; in this case, defective T-cell function. PJP is a severe form of pneumonia.

prenatal diagnosis testing during a pregnancy for specific genetic disorders. Usually performed by 'chorionic villous sampling' – taking a sample of tissue from the developing placenta, and testing DNA obtained from this tissue. Amniocentesis (performed later in pregnancy) is another route to prenatal diagnosis.

rejection rejection by a recipient immune system of transplanted bone marrow or stem cells.

rotavirus a common virus that causes diarrhoea, which can be persistent in children with primary immune deficiency.

sex chromosomes X and Y chromosomes, which determine the sex of an individual. Females have two X chromosomes; males have one X and one Y chromosome. The X chromosome carries several genes that, if faulty, can cause severe immune deficiencies.

stem cells cells from which all blood cells and immune cells are derived.

subcutaneous 'under the skin'. It also refers to anything relating to the loose cellular tissue beneath the skin; for example, an immunoglobulin infusion given directly into the tissue directly beneath the skin is said to be given subcutaneously.

T-cells (or T-lymphocytes) specialised lymphocytes that develop in the thymus, an organ in the chest. They are responsible, in part, for carrying out the immune response.

thrush (candida) a common fungal infection in young infants, often affecting the mouth or nappy area. It can be severe and persistent in children with immune deficiency.

thymus a bow-tie shaped lymphoid organ located behind the upper portion of the sternum (breastbone). The thymus is the chief 'educator' of T-cells. This organ increases in size from infancy to adolescence, and then begins to shrink.

tissue-typing immunologic tests for comparing the antigens on the tissue of a bone marrow transplant donor with those of the recipient (the person who is to receive it). The more closely matched, the better the chance for the transplant to take.

umbilical cord blood blood collected from the umbilical cord after delivery of a baby. Cord blood is a rich source of stem cells that can be banked and used for transplantation of either related or unrelated individuals.

X-linked refers to the inheritance of disorders caused by mutations in genes carried on the X (or female sex) chromosome. This is also known as sex-linked inheritance. In this situation, girls are usually carriers and boys are affected by the condition. Girls inherit one X chromosome from each parent, so have a normal one to compensate for the faulty one. Boys inherit one X chromosome and one Y chromosome, so the effects of the faulty X chromosome are not cancelled out.

X-linked SCID SCID caused by a mistake in an X-linked gene – the 'common gamma chain'. This causes approximately 30 per cent of all cases of SCID.

Notes

www.immunodeficiencyuk.org
hello@immunodeficiencyuk.org
0800 987 8986

About Immunodeficiency UK

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

Support us by becoming a member of Immunodeficiency UK. It's free and easy to do via our website. Members get monthly bulletins.

Immunodeficiency UK is reliant on voluntary donations. To make a donation, please go to **www.immunodeficiencyuk.org/donate**

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

Supported by a grant from the Jeffrey Modell Foundation WIN Program

Jeffrey Modell Foundation | Curing PI. Worldwide.