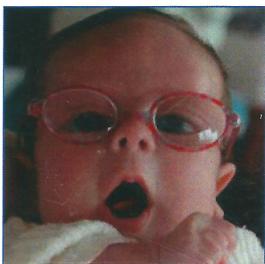
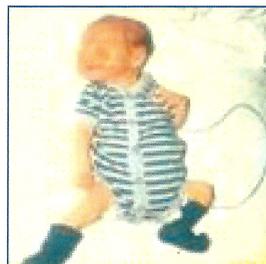


# Lowe Syndrome Trust

**A Guide for Professionals and Families**



**“Care today ... cure tomorrow”**

**LOWE SYNDROME TRUST**

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# Foreword

Oscar, our son, was born on the 26<sup>th</sup> November 1993 at 5.30am following eight years of hoping for a child. During those eight years I had two pregnancies. The first had resulted in a rare pregnancy called a hydatiform mole, which is a growth that forms inside the uterus at the beginning of a pregnancy instead of a foetus. Although in the majority of cases it isn't cancerous, in a few cases – around 2-3 in every hundred – the mole becomes a cancerous tumour called choriocarcinoma. Thankfully, after two years follow up with the Oncology Department, I was given the all clear.

I miscarried at 12 weeks on the second pregnancy and was overjoyed but anxious when I discovered I was pregnant with Oscar.

Sadly the birth did not go well and following a traumatic delivery, we were told during the next few days that Oscar had a VSD (ventricular septal defect, also known as a hole in the heart) and congenital cataracts, which should be operated on within the next few weeks to save his vision.

The next five years were spent attending Great Ormond Street Hospital for various tests to find out whether Oscar had a syndrome. We were told when he was age four that nothing could be found, but were devastated when Oscar was almost six, to find a new DNA test showed he had a rare incurable disease called Lowe syndrome – with a life expectancy of perhaps seven.

Following the trauma of this news and within three months of discovering there was no UK support group or research into the disease, I set up the *Lowe Syndrome Trust*, searched the internet to find professors of medicine to be part of the *Lowe Syndrome Trust Scientific Advisory Board*, lobbied government and enlisted high profile celebrities to help raise awareness of the disease.

Some 11 years later, we have funded numerous Lowe Syndrome research projects both here in the UK and also the USA in the hope of better treatments and a cure. It has been a long, hard and emotional journey, but having a child with the disease takes over any thoughts one might have about giving up.

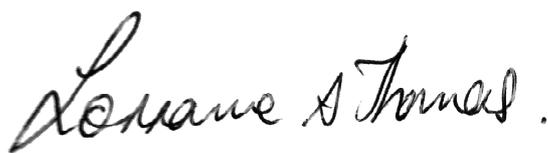
Oscar had progressed really well until the age of 13 when he developed glaucoma, then aged 15 had his first seizure – a day I will never forget when I thought he had died. A few years later Oscar suffered a broken neck of femur (hip) followed closely by a broken knee. With Lowe syndrome, you always are in fear of what each day might bring... kidney wasting, scoliosis, weak bones, weak muscles, blindness, rickets, cysts on the brain, seizures... the list goes on. When we were first told he had a hole in his heart we were devastated, but now this is “just one of the list” of medical problems.

I cannot express the emotion of having a child with a rare incurable disease. Who can offer advice? How do you explain to people why he behaves in the way he does? It has been an incredible learning curve, not just the medical problems, but how life is different when you have a child with “problems”. We have learnt about the education system – or lack of it – for special needs, the waiting lists for speech and language, physiotherapy and occupational therapies. We have learnt the bureaucracy of trying to get help with a child’s behaviour and the complicated issues associated with the State Tribunal System which you must use to get any kind of help for your child. You also learn about the expense of having a child with special needs, holiday clubs work out treble the cost as you have to pay for an assistant to be with him/her... but, that’s what we’re here for, the *Lowe Syndrome Trust* has lots of advice and guidance to offer which we have included in this booklet.

Enough of the negativity.... Would I swap Oscar or wish he was born differently? Well actually, no. Of course we would swap the medical problems for a healthy Oscar. But I cannot explain the love that Oscar brings to us as a family. Lowe children are known to be loving, happy and cheeky little boys, and that is so true.

We hope this book will help you understand more about the disease, but we must stress that symptoms do vary from child to child.

The Trust is happy to discuss any queries you might have – details are below.



Lorraine Thomas

Chair & Trustee

The Lowe Syndrome Trust

Telephone                    0207 794 8858/ 07958 444020

Website                      [www.lowetrust.com](http://www.lowetrust.com)

E-Mail                         [lowetrust@gmail.com](mailto:lowetrust@gmail.com)

Registered Charity        1081241

Registered Address:    77 West Heath Road, London NW3

# 1. Introduction

Low Syndrome (LS) is a rare genetic disorder that results in physical and mental impairment in young boys. The condition has a wide range of symptoms, affecting the eyes, kidneys, brain, central nervous system and musculo-skeletal system – all the result of a single defective enzyme in the body. Affected boys suffer from medical problems throughout their lives and also have special educational needs. Sadly, their life expectancy is reduced due to the many complications of the disease.

## About Low Syndrome

Low Syndrome is named after Dr Charles Low who, in 1952 with his colleagues Mary Terrey and EA MacLachlan at the Massachusetts General Hospital in Boston, first defined the condition. They presented a paper with three case reports of infant boys with a unique group of symptoms not recorded together before – “abnormalities of kidney function, bone disease, mental retardation and congenital glaucoma”.

For this reason Low Syndrome is also known as ‘Oculo-cerebro-renal’ syndrome, because it affects the eyes (oculo-), brain (cerebro-) and kidneys (renal) as a characteristic group of symptoms that appear together (syndrome).

While Dr Low and his colleagues did not know what was causing these symptoms, they had recognised an important group of patients. As the syndrome was only seen in boys, it indicated a genetic defect affecting one of the sex-determining chromosomes: X or Y. In 1992 scientists discovered the defective gene responsible – *OCRL1* – which is on the X chromosome.

Since then, research into Low Syndrome has discovered a lot about how the defective *OCRL1* gene causes the many and varied symptoms seen in affected children, however there is still much we don’t know.

The *Low Syndrome Trust* (LST) was founded in June 2000 by Lorraine and Andrew Thomas following their five year-old son’s diagnosis of Low Syndrome and the discovery that there was neither UK research into this disease, nor specialist support

for families. The aim of the *Low Syndrome Trust* is to fund medical research in the hope of discovering better treatments and eventually a cure.

This handbook is part of the LST's ongoing work to support families by:

- ensuring families are as well-informed as possible
- providing information to health professionals, who may know very little about the disease
- increasing understanding of this condition for anybody who may encounter a child with Low Syndrome.

This handbook offers information about:

- the medical effects of Low syndrome and the treatments
- the educational needs of children with Low syndrome
- the effects that living with Low syndrome can have on a family
- current research into the disease
- useful contacts for parents and professionals dealing with Low syndrome.

Our vision is to provide the best help and support possible to children and young people affected by Low syndrome, by keeping parents well-informed and helping them work together with caring professionals.

Whether you are a parent or family member of someone with Low Syndrome, a teacher, or healthcare professional, we hope that you find this handbook useful. Some of the information in this booklet is quite technical and some of it may seem very daunting. Use it as a resource to dip into when you need to, discuss it with your medical team, friends and family, and feel free to contact the *Low Syndrome Trust* if you want to discuss anything you read.

**[www.lowetrust.com](http://www.lowetrust.com)**

For more information about Low syndrome, and UK events please visit our award-winning website [www.lowetrust.com](http://www.lowetrust.com)



## Low Syndrome RaDaR Group

The UK Registry for Rare Kidney Diseases (RaDaR: <http://rarerenal.org/radar-registry/>) has now officially registered a *Low syndrome/Dent disease RaDar Group*, including the creation of a knowledge bank (a medical database, known as a registry), where we can gather together data on Lowe/Dents (<http://rarerenal.org/rare-disease-groups/dent-low-rdg/>). By sharing information we can begin to study the bigger picture of Lowe syndrome/Dent disease in the UK. The more data we can gather, the clearer the picture we will get of how the disease progresses, which areas are being treated well and which areas need more research and attention.

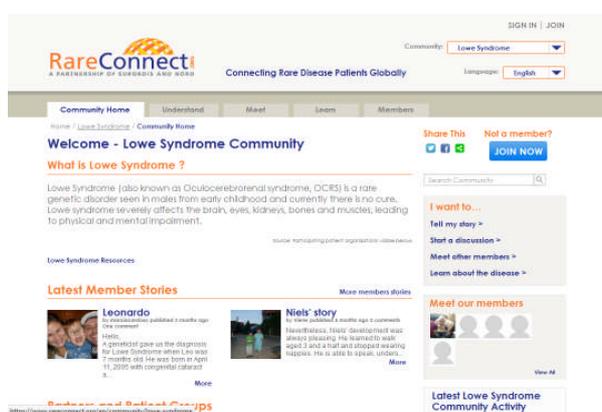
Pooling our knowledge will be vital in identifying important areas to fund scientific and medical research, and provide a contact point for clinicians interested in forming clinical trials. This will make us better able to care not only for of existing patients, but also the future ones yet to be born, and eventually to find a cure.

## European Alliance of Low Syndrome

In December 2012 the UK-based LST joined forces with similar associations of families affected by Lowe syndrome from Spain, France, Italy and Germany to create the *European Alliance of Low syndrome*. The European Alliance of Low Syndrome aims to strengthen the cooperation between patient's families, doctors and researchers around the world to get a better understanding of Lowe syndrome and to guide further medical research. This is a rare initiative for such a rare disease that affects approximately 300 families in Europe.

In partnership with EURORDIS, the voice of rare disease patients in Europe, the European Alliance of Low Syndrome has developed an online social network community for people affected by Lowe syndrome using the collaborative RareConnect platform.

To visit the EURORDIS RareConnect Low syndrome community website, visit [www.rareconnect.org](http://www.rareconnect.org) and look for 'Low syndrome' under the 'Community' list, or search for *Low syndrome RareConnect*.



The European Alliance of Lowe Syndrome incorporates:



**Spanish Lowe Syndrome Association**  
(Asociación Síndrome de Lowe España)

[www.sindromelowe.es](http://www.sindromelowe.es)



**French Lowe Syndrome Association**  
(Association du Syndrome de Lowe)

[www.syndrome-lowe.org](http://www.syndrome-lowe.org)



**Italian Lowe Syndrome Association**  
(Asociatione Italiana Sindrome di Lowe)

[www.aislolowe.it](http://www.aislolowe.it)



**German Lowe Syndrome Association**  
(Lowe-Syndrom e.V.)

[www.lowe-syndrom.de](http://www.lowe-syndrom.de)

The Lowe Syndrome Trust also partners with the US Lowe syndrome charity, the *Lowe Syndrome Association*



**The Lowe Syndrome Association**

[www.loweassociation.org](http://www.loweassociation.org)

## 2. Lowe Syndrome – FAQ

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### 2.1 Questions & Answers

**Q: What is Lowe Syndrome?**

A: Lowe syndrome (LS - also known as Oculocerebrorenal syndrome, OCRS) is a rare genetic disorder seen in males from early childhood. Lowe syndrome severely affects the brain, eyes, kidneys, bones and muscles, leading to physical and mental impairment, and currently there is no cure.

Lowe syndrome was named after Dr Charles Lowe, who was the first to describe it in 1952.

**Q: What causes Lowe syndrome?**

A: Lowe Syndrome is caused by mutations in a gene (known as *OCRL1*) that results in the deficiency of an enzyme called phosphatidylinositol 4,5-biphosphate 5 phosphatase (which we will call the ‘LS enzyme’). Mutations in *OCRL1* can cause the LS enzyme either to not work properly, or to not be produced at all. The function of the LS enzyme is essential for normal metabolic processes that occur in a part of the cell called the Golgi apparatus.

This LS enzyme deficiency leads to various developmental defects including cataracts and problems in the brain and kidneys. How the loss of LS enzyme activity leads to these defects is not yet completely understood.

**Q: Why can’t the missing/faulty enzyme just be replaced?**

A: Scientists must first better understand the subtle biochemical imbalance caused by the defective enzyme. It is possible that overcorrection could be just

as harmful as having the faulty enzyme. Furthermore, there is currently no method available to target therapies specifically to the areas of the cells where the LS enzyme is located. As the missing enzyme impacts a number of tissues all over the body, it would be very difficult to effectively target gene therapy.

**Q: Why do only boys get Lowe syndrome?**

A: The gene that is mutated in Lowe syndrome is found on the X chromosome (also called 'X-linked'). Females have two X chromosomes, and so have two copies of the *OCRL1* gene, whereas males have one X (and one Y), so only have one copy. If a brother and sister both have a faulty copy of the gene, the boy will have Lowe syndrome, as his only copy is defective, but the girl will not have Lowe syndrome, as she also has a fully functional copy of the gene.

It is possible but extremely rare for girls to have Lowe syndrome when both copies of the *OCRL1* gene are faulty, but almost all cases are in boys.

**Q: How does someone 'get' Lowe syndrome?**

A: Lowe syndrome can occur either through inheritance of a defective copy of the *OCRL1* gene, or via a spontaneous genetic mutation.

In inherited cases, boys inherit the defective gene from their unaffected mother.

In spontaneous cases, Lowe syndrome arises as the result of a new mutation and the mother does not have a defective copy of the gene.

Whether a mother has a defective copy of the gene can be determined by genetic testing. The *OCRL1* gene is located on the X chromosome, meaning that it is 'X-linked' and mutations in it predominantly affect boys. Females who have mutations in the *OCRL1* gene are known as 'carriers'; there is a chance they will pass the defective gene to their children, but they are not affected by the syndrome themselves.

**Q: Can Lowe syndrome be prevented?**

A: In families where a case of Lowe syndrome occurs, female relatives can be tested to find out if they carry the defective gene as they may be at risk of having a son with Lowe syndrome. A 'slit-lamp eye examination' is currently used to help determine whether a woman carries a mutation in *OCRL1*; this may be used in conjunction with a DNA test for the specific mutation shown in the family. Various family planning options are available, including having tests before your baby is born (prenatal testing). Families should consult with a geneticist to learn more about their options at the earliest opportunity.

**Q: How is Lowe syndrome diagnosed?**

A: The characteristic cataracts and low muscle tone (hypotonia) seen in Lowe syndrome are detectable at birth or shortly thereafter and offer an early indication of the disease. A DNA test can be carried out by a specialist laboratory in the UK. Depending on the type of mutation, a skin test may also be needed for a definitive diagnosis. In this instance, a skin sample is taken and sent for analysis at a laboratory in America. Some individuals may choose to have blood drawn and sent for testing to determine the DNA mutation of the gene. Prenatal diagnosis is also available at some labs. Physicians and families should contact the *Lowe Syndrome Trust* for further information on these tests.

**Q: What are the common features of Lowe syndrome?**

A: Cataracts in both eyes, found at birth or shortly after.  
Poor muscle tone (hypotonia) and delayed motor development.  
Glaucoma (in about 50% of cases).  
Intellectual disability, ranging from borderline to severe (in a few cases intelligence may be normal).  
Seizures (in about half the cases).  
Significant behaviour problems (in many, but not all, cases); children are often on the autistic spectrum.  
Kidney involvement ('leaky' kidneys, or renal tubular acidosis).  
Tendency to develop rickets, bone fractures, scoliosis, joint problems.  
Short stature.  
Cysts - Kidney, brain and skin  
Undescended testes.  
Constipation.  
Dental problems.  
Life span may be shortened due to progressive kidney failure, although death may occur at earlier ages due to other causes. Life expectancy will likely increase as knowledge increases and new treatments are developed.

**Q: How is Lowe syndrome treated?**

A: There is no cure, but many of the symptoms can be managed effectively through medication, surgery, physical and occupational therapies, and special education. Nutritionists can also play a beneficial role in helping to outline and suggest appropriate diets.

**Q: What research is underway?**

A: In 1992 the gene that causes Lowe syndrome was discovered. In 1995 researchers found that the genetic defect causes an enzyme deficiency. Since the LST was founded, several research teams have been funded in the UK and worldwide to investigate the function of the gene and the protein it codes for, to better understand the biochemistry of Lowe syndrome. There is a great deal of research ongoing and the LST organises an International Symposium every two years to facilitate the sharing of research. Other areas of research in recent years include behaviour problems and clinical care. Information about current research can be found in this booklet, or you can contact the LST for a current fact sheet.

**Q: What are boys with Lowe syndrome like?**

A: Generally, they are affectionate and sociable, love music, and have a great sense of humour. However, they may also suffer from serious behavioural problems.

**Q: How many boys are there with Lowe syndrome?**

A: Lowe syndrome is a rare disease. It has been identified in most cultures around the world and seems to have the same frequency in all populations, although no one knows exactly how many individuals globally have Lowe syndrome. The precise mutation that causes the disease varies from family to family – over 65 different mutations of the *OCRL1* gene have been identified in the UK so far – and the disease varies in its symptoms and severity. There is currently no detailed documentation on the number of living individuals or deaths related to Lowe syndrome, however families will often notify the LST when an individual has died due to complications of Lowe syndrome. Ages of known deaths have ranged from 19 months to 56 years old.

## 2.2 Lowe Syndrome Timeline

Every child with Lowe Syndrome is different but this summary gives a quick overview of some of the main medical features and an indication of when they might appear. **It should be considered a rough guide and not necessarily a comprehensive one.**

<b>Birth</b>	Cataracts, hypotonia
<b>0-teens</b>	Corneal degradation (50%) – keloids
<b>0-1 years</b>	Fanconi syndrome (kidneys) becomes apparent (if not, kidneys should be tested 3 monthly so that it is detected in a timely fashion).
	Loss of deep tendon reflexes (e.g. knee jerk).
	Undescended testicles
<b>3-4</b>	Rickets may develop
<b>0-10 years</b>	Glaucoma may develop (50%) Febrile convulsions Nystagmus/strabismus
<b>6 onwards</b>	Bone fractures (as boys learn to walk)
<b>10 onwards</b>	Kidney failure may commence
<b>Older children</b>	Major motor/generalised convulsions
<b>8-13 years</b>	Likely to be a time of particular behavioural difficulties
<b>Early teens - adulthood</b>	Development of scoliosis (50%) Joint swelling and arthritis
<b>Throughout life</b>	Increasing risk of hernias



## **3. Parents and Families: Living with Lowe**

Raising a child can be a wonderful and challenging experience; raising a child with severe disability raises even more challenges but there will also be positive experiences along the way and this should not be forgotten. In this section, we will discuss how having a child with Lowe syndrome may impact upon a family and offer some advice based on parents' past experiences. Every family is different and, although small, there is a network of families affected by Lowe syndrome who are there to share experiences with.

Lowe syndrome presents many difficulties for families as the children not only have complex medical problems but also have special educational needs (SEN). Parents will have to deal with complex medical problems, with an often-unfamiliar special education bureaucracy and with raising a child whose development is slow and erratic and whose behaviour may disrupt family life.

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### 3.1 Diagnosis and early years

Parents usually learn that there is something wrong shortly after birth when their new born child is diagnosed with cataracts and often hypotonia ('floppy baby' syndrome). As most doctors are not familiar with Lowe syndrome, many families (especially those with no history of Lowe syndrome) experience long and frustrating delays before receiving the diagnosis and the beginning of treatment of this rare and little known condition.

Not long after birth, the child is likely to need a cataract operation. In the first two years, regular tests are needed to pick up the onset of kidney problems. The stress of having a new baby and having to deal with medical problems and the complications and uncertainties of diagnosis can be very difficult and it is important to develop strategies for coping with the emotional impact along with the immediate practical problems. The *Lowe Syndrome Trust* can help by supplying contacts for help and guidance and by providing information.

### 3.2 Growing Older

Boys with Lowe syndrome are often warm and loving but they can also be distant, sharing some similarities to autism. They are wonderfully curious but are given to exhaustive conversation. Often happy and cheerful, they can also be obstinate and forceful in trying to get what they want and can provoke a crisis at any moment in any place. Their behaviour is on the autistic spectrum and their educational and daily needs can be extremely challenging.

Having a child with so many special needs places extra demands on time, energy, and money. A family can easily become socially isolated and emotionally drained, focusing all its attention and energies on caring for the child. While parents continue to have emotional "ups and downs" over the years, experience helps them make the adjustments needed to meet the needs of their son, their family, and themselves. Experienced parents offer the following bits of advice to help new parents keep things in perspective and maintain a healthy and realistic attitude.

### 3.3 Advice for parents

It is immeasurably useful for you as parents to become as knowledgeable about Lowe syndrome as you can. It may well be the case that you find yourselves providing information to health professionals and care workers unfamiliar with the condition. Siblings will also need to understand their brother's condition. They should know its name and that it is not contagious. As they get older they should be told how Lowe syndrome is inherited and the implications for their own children. If they are involved, extended family and friends should be given as much information as

possible so that they can understand the child's condition and be supportive. It is also important to seek professional advice and where possible put developmental programmes such as speech and language therapy, physiotherapy and occupational therapy in place to help your child's development.

Remember that progress will be slow.

Listen to the concerns that other family members have and keep them informed. Involve the whole family in caring for the child if possible. If you have other children, help them to understand their brother's condition and the extra attention that he needs but that this doesn't mean you love them any less. Giving them opportunities to help can make them feel grown up and an important part of the family. Siblings can provide wonderful stimulation and companionship and, because of their unique perspective, are sometimes able to offer surprisingly helpful suggestions.

### 3.4 Support

Getting to know other parents who have children with disabilities or chronic illness can be very positive and an invaluable source of advice and support. In addition, a community group is a valuable resource in finding out about local programs and services. Learn about the rights of people with disabilities. You can be your child's best advocate as well as an advocate for other children.

As much as possible, try to keep a sense of humour. Sometimes the most effective way of dealing with a difficult situation is to try to find something funny in it.

Understand that the many emotions you feel are normal, including grief, fear, anger, and despair. There is no right or wrong way to feel. What is important is how you choose to cope with your feelings. Fear and anger, for instance, can lead to paralysis or they can lead to productive action.

Parents of children with severe learning difficulties and autism report more stress and mental health problems than parents of children without disability. Furthermore, the stress tends to be chronic and persists over long periods of time. Interestingly, behavioural problems of disabled children are more closely linked to parental stress than the severity of the disability itself, so learning the skills for managing challenging behaviour may be crucial to the long-term well-being of a family (See Beck and Hasting, 2004). Psychological therapies such as Cognitive Behavioural Therapy (CBT) may also help parents to cope with the stress of daily life.



## 4. Medical Features

Lowes Syndrome is a very rare disease (1 case in every 500,000 of the population although accurate figures are not available). It affects males, while females may be carriers of the faulty gene. This is because the gene is on the X chromosome (from mother to son). To date, research into this disorder has been very limited. This section describes the more common and well documented signs and symptoms of Lowes syndrome. It is not meant to be comprehensive, because different children will show the signs or symptoms listed below to a greater or lesser extent and their severity will also vary from one child to another. Great Ormond Street Hospital is the centre of clinical knowledge about Lowes Syndrome in the UK.

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## 4.1 Diagnosis

### *At Birth*

A doctor considers a diagnosis of Lowe syndrome when there are *cataracts* in both eyes at birth and low muscle tone, or *hypotonia* (floppy baby syndrome), especially if there is a family history of the condition.

Diagnosing Lowe syndrome early in infancy is not always straightforward. Although cataracts and hypotonia are detectable at birth or shortly afterwards, further symptoms in eyes, kidneys and nervous system may only develop later. As Lowe syndrome is so rare, health care professionals are not familiar with the disease and so it may not always be recognised straight away.

### *DNA sequencing*

Lowe syndrome may be diagnosed by DNA testing, which requires a blood sample to sequence the DNA of the LS gene (see [Section 4 - Genetics](#)). However, in some cases, depending upon the type of mutation, this may not yield a sufficiently clear answer.

### *Skin sample*

Definitive diagnosis of Lowe syndrome can be made by testing for a specific enzyme in skin cells. In this procedure, a small skin sample is taken from the patient, usually by a local GP. The sample must be sent to a specialised biochemistry laboratory for culture and analysis. The skin biopsy may need to be taken under sedation due to the behavioural problems of many children with Lowe syndrome, and for this reason it is only used when necessary. For more information on testing, see [Section 4 – Genetics](#).

## 4.2 Eyes

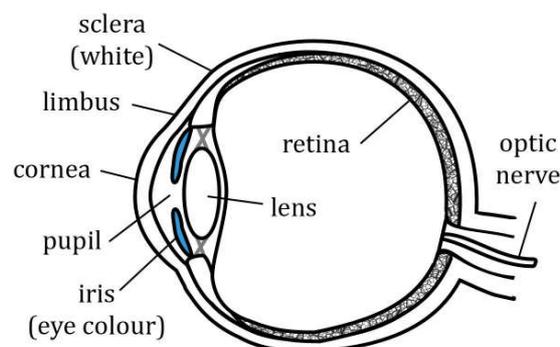


Figure 1. Diagram of the eye

The ocular (eye) features of Lowe syndrome include:

- congenital (present at birth) *cataracts* (in almost 100% of cases),
- *glaucoma* (in 50% of cases)
- *corneal degeneration*
- *retinal detachment*
- *strabismus* (crossed eyes)
- *nystagmus*.

The effectiveness of treatments for these conditions varies, and any of these conditions may cause significant visual disability. In some rare cases in which the eye has become blind and severely painful, surgical removal of the eye, called enucleation, may be an option.

#### 4.2.1 Eye examinations

All individuals with Lowe syndrome should have their eyes dilated and carefully examined by an ophthalmologist every 6-12 months. The main reasons are:

- the risk of retinal detachment increases after cataract surgery
- most individuals with Lowe syndrome will not complain about loss of vision from retinal detachment
- the high risk of glaucoma in Lowe syndrome.

Due to the complications of Lowe syndrome, in over 50% of the boys it is necessary for these check-ups to occur under anaesthesia – pressure measurements in a crying infant are notoriously unreliable. If the child is able to cooperate when he is older, examinations in the ophthalmologist's office may be possible.

#### 4.2.2 Cataracts

In affected males cataracts are usually present at birth, although they may not be discovered until the child is several weeks old. A cataract is a painless 'clouding' of the lens of the eye. The lens is normally clear and transparent, like a camera lens and has a similar function. It focuses light onto the *retina*, which is at the back of the eye. The retina is like the camera film and records the image of what we see, which is then transmitted by the *optic nerve* to the brain, where it is processed. A cloudy lens reduces the amount of light that can reach the retina, so images are not seen clearly.

It is important to remove cataracts as early as possible, preferably within the first few days or weeks of life, so that the baby can learn to see normally. If the cataract is not removed until later in life, the visual system may not learn to process images properly and the eye can be left blind. Early cataract removal facilitates proper development of the visual system. The major factor determining the time to operate on congenital cataracts is the health of the infant - in some places, paediatric anaesthesia is not available to put newborns to sleep safely for the duration of the operation.

### *Cataract Operations*

In the cataract operation, the abnormal cloudy lens is removed surgically under a general anaesthetic. A small opening is made in the eye, typically at the edge of the zone where the clear cornea joins the white of the eye (called the *limbus*). Microscopic instruments are inserted into this opening to cut up and fragment the cataract and to remove the small pieces.

This operation improves the passage of light through the eye. However, as the lens has been removed, the eye cannot focus light onto the retina, and strong glasses or contact lens must be used to compensate for this. For most children removal of the cataracts and correction using glasses or contact lenses leads to a substantial improvement in vision.

### *Artificial lenses*

Surgical implantation of artificial [plastic] lenses is usually not recommended for several reasons. These include: the small size of the eyes of infants and the inability to reliably predict the 'adult size' of the eyes later in life; the possible complications from glaucoma, which has a high rate of frequency in Lowe syndrome; the risk of other complications of surgery; the uncertainty of long-term stability of artificial lenses in infants in general; and the possibility of problems with the cornea in Lowe syndrome. With any procedure that involves surgically opening the eye, implantation carries risks, such as infection, loosening of the lens, lens rotation, inflammation, increased risk of glaucoma, and an increased possibility of retinal detachment.

A few individuals have had lens implants: an artificial lens is a lens implanted into the eye, replacing the original human lens which the cataract has made opaque. The implanted lens usually consists of a small plastic disc with plastic side struts to hold the lens in place. An artificial lens that is implanted years after the original cataract removal (called a 'secondary lens implant') must be sutured in place to remain stable.

Although ophthalmologists are investigating implantation of new types of artificial lenses in infants, the real and substantial complications in Lowe syndrome make such implantation highly investigational at this time.

### **4.2.3 Glaucoma**

Glaucoma develops in about half of the boys affected with Lowe syndrome. Glaucoma is a disease in which the pressure inside the eye becomes high and can damage the retina and optic nerve, leading to loss of sight. Sustained, elevated pressure can cause the infant eye to enlarge abnormally because, unlike an adult eye, the outer coats of the eye (the white part, called the *sclera*), is relatively thin and stretchable under the increased pressure. Historically, this condition is called *buphthalmos* (literally, 'ox eye' because of the large size of the eye).

Treatment of infantile glaucoma is difficult. Medicinal eye drops may be tried first to try to lower the pressure, but they are rarely effective by themselves. If eye drops do not work, various surgical procedures may be tried. Laser treatment (diode laser) can

be used to reduce the amount of fluid the eye makes. A new channel can be created to allow the fluid inside the eye to leave more easily and thereby lower the pressure. Sometimes an artificial valve with a small tube is sutured into the front of the eye to control release of fluid and thus decrease the pressure. Unfortunately, in some cases glaucoma is so severe it cannot be controlled, ultimately causing the eye to become completely blind.

The risk of glaucoma is the major reason for routine examinations of the eyes during infancy and childhood – see [4.2.1 Eye examinations](#). Although the risk of glaucoma lessens considerably after the first year, it may develop even after 10 years of age, hence the need for regular check-ups.

#### 4.2.4 Corneal degeneration

The cornea is the clear ‘watch glass’ cover on the front surface of the eye that covers the iris and the pupil. By their teens about half of boys with Lowe syndrome develop what appears to be scar tissue, often called a *keloid* or *fibroma* over the cornea on either one or both eyes. (Some physicians believe that this growth is not a true keloid but probably represents a fibroma or benign growth of fibrous tissue which resembles a growing scar.) The reason for this is not known, but like a cataract, it can impair vision and may need to be surgically removed.

Keloids may be removed surgically but tend to recur. In addition, surgical removal may leave a scar that cannot be managed without creating more scarring. To date, medical treatment has been unsuccessful, and in many cases, keloid formation results in progressive and severe visual impairment, despite all treatments.

##### *Corneal Transplants*

Corneal transplants have been done in a small number of individuals with Lowe syndrome. However, corneal transplantation is not recommended because of the difficulties with post-operative management, including drops to suppress rejection of the transplant, numerous examinations and management of the associated problems. Post-operative evaluation and care is difficult in children in general and even more so in individuals with Lowe syndrome.

A corneal transplant can be done with either a donor cornea or a synthetic cornea. When choosing to undergo a corneal transplant, the purpose and risks of doing the transplant must be determined –if the purpose is to improve visual acuity, then the outcome depends on the health of the eye and what the visual acuity was prior to corneal degeneration.

As with all surgeries there are risks associated with the corneal transplant, which include infection and possible rejection of the donor cornea. Corneal transplants in infants and children are much less successful than those in adults, and so transplants should be the last option in management for corneal diseases in Lowe syndrome.

### 4.2.5 Strabismus

Many children with Lowe syndrome develop a squint (*strabismus*) or crossed eyes, a condition in which the eyes are not aligned and do not move together properly. In infants this usually means that one eye is turned in. In infancy it can adversely affect the development of visual systems in the brain and impair eyesight.

Treatment involves a complete assessment of the movements of the eyes and their muscles, eyesight and prescription of the right sort of glasses. Treatment continues by patching one eye (usually the preferred or straight eye), in order to force improvement in the 'lazy' eye with the poorer sight.

As soon as the child can follow a target equally well with each eye, surgery is performed on the muscles of the eyes to align them. If vision is equal, there is a good chance that the eyes will remain aligned after surgery. After surgery for strabismus the child should be followed carefully for any recurrence of the problem.

### 4.2.6 Nystagmus

The term *nystagmus* refers to an uncontrollable and rhythmical movement of the eyes. While nystagmus by itself does not cause loss of vision, it is often caused by conditions related to poor vision, and occasionally can be caused by changes in brain function.

The genetic defect that causes Lowe syndrome can also affect the development of the retina in the eye. Unfortunately, there is no good permanent treatment for nystagmus, aside from taking all possible steps to develop and retain good vision from an early age, as described above.

### 4.2.7 Enucleation

Under very rare circumstances when an eye has become blind and painful, it may need to be removed to help ensure that the face develops normally, by a procedure called *enucleation*. After the eye is removed, the ophthalmologist will implant a ball to maintain the volume inside the orbit and to stimulate normal growth of the facial bones and eyelids.

After several weeks of healing, a 'glass eye' shell is fitted over the healed surface. Recently developed surgical techniques use newer materials that provide better movement of the artificial shell. Because the shell is primarily cosmetic, its use is optional. Some parents may decide against the use of an artificial shell for their child, particularly if the child's level of cooperation is less than optimal.

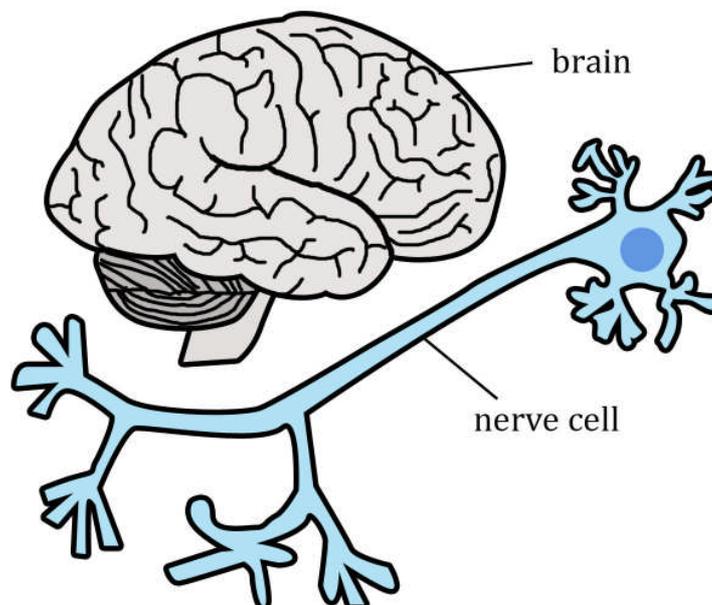
### 4.2.8 Optical devices

A variety of optical devices have been used by individuals with Lowe syndrome. Most individuals report the use of glasses. Contact lenses are used by about half of all individuals.

In addition, some individuals have used magnifiers, monacles, strix machines, telescopes and Zoom Text software.

## 4.3 Brain and central nervous system

The nervous system includes the brain, spinal cord and nerves, and it controls the muscles. Lowe syndrome causes problems in most of these areas, including intellectual impairment, seizure disorders, behavioural problems, physical changes in the brain and *hypotonia* (poor muscle tone).



### 4.3.1 General learning difficulties

The extent of learning difficulties in individuals with Lowe syndrome varies widely. Between 10-25% of individuals have an IQ at the lower end of the 'average' range, and another 25% have mild to moderate general learning difficulties. Others have severe learning difficulties. Although it is not possible to predict learning ability at birth, intelligence appears to be stable over the life span of most individuals. Therefore, it is important for parents, caregivers and healthcare professionals to seek services for individuals with Lowe syndrome as early as possible

### 4.3.2 Seizure disorders

Seizures occur in about half of all boys with Lowe syndrome.

- Younger children may have febrile convulsions (seizures caused by fever). These do not usually require medication unless they recur.
- In older boys, seizures are usually of a major-motor or generalised type.

Individuals with seizure disorders will need an EEG (electroencephalogram) test to detect abnormal brain wave patterns, which may help locate the place in the brain where the seizures begin, and assist in diagnosis and treatment.

In many cases, these seizure disorders respond well to medication (anticonvulsants or antiepileptic drugs, also known as AEDS).

Some individuals develop 'refractory' or 'resistant' epilepsy or seizures that are difficult to control. The use of a vagus nerve stimulation device, or 'pacemaker for the brain', is under investigation for individuals with Lowe syndrome. This device consists of an implanted generator and a nerve stimulation electrode which transmits antiepileptic electric signals to the brain through the vagus nerve in the neck.

#### Types of seizures

All seizures are the result of abnormal electrical disturbances in the brain. A seizure is defined as: the physical findings or changes in behaviour that occur after an episode of abnormal electrical activity in the brain.

Seizures are classified into two categories: generalised seizures and partial seizures.

#### 1) Generalised seizures

Generalised convulsive seizures can be classified as *atonic*, *tonic*, *clonic*, *tonic-clonic*, *myoclonic* or *absence*, based on the clinical symptoms and EEG abnormalities.

- *Tonic / clonic seizures*  
In tonic seizures, the muscles contract, including respiratory muscles, usually for a brief time. Clonic seizures involve rhythmic shaking or spasms without rigidity of the muscles and are longer than tonic seizures.
- *Grand mal*  
When combined, a generalised tonic-clonic seizure is also called a grand mal seizure. A generalised tonic-clonic seizure is a seizure that involves the entire body. Such seizures usually involve rigidity of a person's muscles, violent contractions of the muscles and loss of consciousness.
- *Atonic seizures*  
An individual who experiences an atonic seizure loses muscle tone. At times, it may affect only one part of the body or it can affect the whole body. When the whole body is affected, the person can suddenly fall, also known as a 'drop attack'.

- *Myoclonic*  
Myoclonic seizures are seizures that involve brief jerky contractions of certain muscle groups, generally the face and trunk portion of the body.
- *Absence seizures*  
In an absence seizure, the individual may appear to be staring off into space with or without twitching movements of the eye muscles. This type of seizure usually lasts just a few seconds, but can last for a few minutes in length.

## 2) Partial seizures

Partial seizures occur when seizure activity occurs in a limited area of the brain. Partial seizures can be further defined as *simple*, which do not affect awareness or memory, or *complex*, which affect awareness or memory of the events before, during and immediately after the seizure and affect the individual's behaviour.

- *Simple partial seizures*  
During a simple partial seizure an individual does not lose consciousness, but may experience jerking movements, tingling, or odd mental and emotional events, including déjà-vu, mild hallucinations, or extreme responses to smell and taste. After the seizure, they may experience weakness in certain muscles.
- *Complex partial seizures*  
Complex seizures that occur in the temporal lobe can cause loss of judgment, involuntary or uncontrolled behaviour, or even unconsciousness. Patients may lose consciousness briefly and appear to be staring into space. Emotions can be exaggerated; some individuals may appear to be in a drunken state. Repetitive movements may appear with this type of seizure, such as chewing or smacking of lips. Seizures usually last no more than 2 minutes and can occur infrequently, or as frequently as every day. Sometimes a throbbing headache may follow a complex partial seizure.
- *Secondary, generalised seizures*  
Simple or complex seizures may change into generalised seizures if the seizure spreads out from its origin. A generalised seizure affects the whole brain.
- *Generalised, soft tremors*  
Tremors involve involuntary rhythmic movements of muscles. The most common body parts affected are the hands, head, facial muscles, vocal cords, trunk of the body and legs.

## Other questions

Q: *Are seizures dangerous?*

A: Seizures almost always stop on their own, without any medical attention. Perhaps the biggest problem with a seizure in public is that they cause bystanders, who are well-intentioned, to panic. An ambulance is rarely needed, and only if the seizure is not stopping on its own. Ask your doctor for a 'time limit' for when to call an ambulance – this varies with seizure type and

other factors. Usually just protecting the patient from hurting himself during the seizure is all that is needed.

*Q: My son was just diagnosed with epilepsy, and I am afraid to leave him, even at night, or to go anywhere. How does life get back to normal?*

*A:* All parents have this fear, and the good news is that over time (usually a few weeks) you relax and life *does* get back to normal. The biggest family problem with seizures is the uncertainty of not knowing when the next seizure will occur, or even if it will occur. Eventually most families decide to refuse to let this uncertainty ruin their life.

*Q: Do seizures damage the brain?*

*A:* This is highly controversial, and the short answer is that for most seizure types we don't know. The current majority opinion among neurologists is that repeated seizures do cause slight neuronal injury over time. However, this depends on so many other factors that in a given patient there is not usually any noticeable adverse effect, even in patients with uncontrolled seizures over many years. Clearly though, it is best to try to control seizures if possible.

### **4.3.3 Behaviour problems/Autistic Spectrum Disorder (ASD)**

Although boys with Lowe syndrome are often happy, loving and very sociable, many also have a characteristic pattern of behaviours that may interfere with everyday functioning. These include temper tantrums, stubbornness, unusual repetitive movements (especially of the hands), inability to concentrate or focus, and unusual obsessions or preoccupations. Some individuals may become violent and self-abusive. These behavioural patterns are thought to be a specific feature of Lowe syndrome. Some evidence suggests that for many individuals, the most difficult period for behaviour problems is between the ages of 8-13 years. In some cases, however, severe behaviour problems continue into adulthood. Behaviour modification techniques may be helpful for some boys and in some cases medication therapy may be effective. Some individuals have experienced improvement with the help of antidepressant and/or antipsychotic medications.

Early intervention is key in managing behaviour. There are many different educational approaches for children with ASD and the most appropriate varies from child to child. Advice may be sought from your Local Education Authority (LEA) or from various autism charities. See also the section on behaviour in *Chapter 5* below.

### **4.3.4 Physical changes in the brain**

Brain images generated by MRI (magnetic resonance imaging) may demonstrate abnormalities in the brain's white matter. These abnormalities are caused by tiny fluid-filled cysts which develop during the first year of life. Whether this is a cause or

an effect of impaired brain function is unknown as yet. Brain atrophy, or shrinkage, has also been reported.

#### 4.3.5 Hypotonia / Scoliosis

Hypotonia, or poor muscle tone, is always present at, or soon after, birth. Hypotonia results in a ‘floppy’ appearance and poor muscle strength. During infancy, hypotonia causes problems with head control and feeding (due to poor sucking). As the boys grow up, motor development is generally delayed in most areas. For instance, learning to walk is usually significantly delayed – about 25% of boys with Lowe syndrome develop the ability to walk alone between 3-6 years old. By the age of 6-13, 75% of boys with Lowe syndrome have developed the ability to walk.

Although hypotonia improves slowly with age, most individuals do not reach normal muscle tone or strength, and related problems can occur as they grow older. Loose or hypermobile joints are also common due to the poor muscle and tendon strength. About half of all affected boys will develop *scoliosis*, or curvature of the spine, due to weakness in the back muscles. The greatest risk for developing scoliosis occurs during the early teenage through adult years. There is also an increased risk of developing hernias throughout life due to weak abdominal muscles. Eating problems may also result from poor muscle tone (see [Section 5.1.4. Eating problems](#)).

Hypotonia in Lowe syndrome is due primarily to nervous system dysfunction. Individuals have a slight elevation of a muscle enzyme called *creatinine kinase* in their blood. Special muscle tests, such as EMGs (electromyographs) or muscle biopsies, typically have normal or minimally abnormal results and are not needed to establish a diagnosis of Lowe syndrome. Deep tendon reflexes (such as the knee jerk) are usually absent by 1<sup>st</sup> birthday. This may be due to nerve damage, which has occasionally been detected, but may also be due to nervous system dysfunction in the spinal cord. The absence of these reflexes causes no interference with normal function. The most effective treatment for hypotonia is physiotherapy, begun early in infancy if possible.

#### 4.3.6 Umbilical hernia

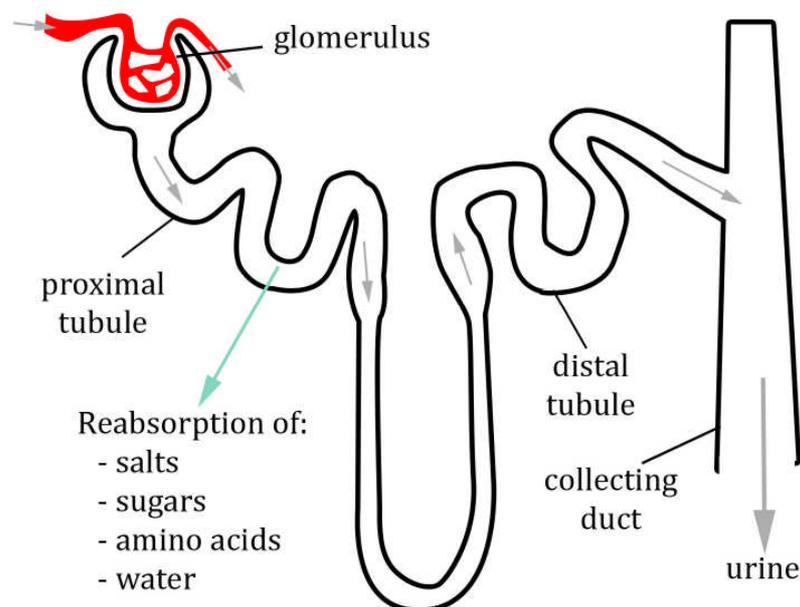
Typically the umbilical gap closes prior to birth, but if it fails to close at birth, due to the poor muscle tone in Lowe syndrome boys, tissue may bulge through the weak area in the abdominal wall around the navel, resulting in an umbilical hernia. While usually present at birth, this may not be noticeable until the umbilical cord stump has fallen off. Diagnosis of an umbilical hernia can be done by a physician through examination of the abdomen and evaluating size, shape and appearance of the hernia.

Most umbilical hernias may close on their own without treatment (by age 5 years in the general population). Surgery may be needed to repair an umbilical hernia that has not closed on its own. The likelihood that an umbilical hernia will heal on its own depends in part on how the muscle tone improves and how large the hernia is.

## 4.4 Kidneys

The kidneys work as filters, cleaning the blood. In normal kidneys, the blood is filtered by many tiny filters, each one called a glomerulus (plural: glomeruli), which are attached to tiny tubes, called tubules, that empty into larger collecting tubes and form the urine that is excreted every day.

After filtering, the liquid filtrate passes through the tubules where important molecules and substances that the body needs, such as salts, sugars, amino acids and water, are re-absorbed back into the body. The waste products and some water that are left are passed out as urine. The part of the tubule closest to the glomerulus is called the proximal tubule and is the most active site, accounting for about 85% of the re-absorption done by the kidney.



### 4.4.1 Renal Fanconi syndrome

#### *Kidney 'wasting' and replacement therapy*

The primary kidney problem in Lowe syndrome is the abnormal 'wasting,' or loss, of certain substances into the urine, including: bicarbonate, sodium, potassium, calcium, phosphate, amino acids, organic acids, albumin and other small proteins, L-carnitine, and the obligatory loss of a large volume of urine fluid associated with the loss of these substances.

In kidneys affected by Lowe syndrome, the proximal tubules are abnormal. As a result, the filtered substances named above are not reabsorbed normally and end up being excreted, or 'wasted', in large amounts in the urine. This reabsorption problem is generally known as *Fanconi-type renal tubular dysfunction*, named after the Swiss paediatrician Dr. Guido Fanconi, who first described the condition in another

disease. Fanconi syndrome is known to occur in several other genetic diseases and syndromes besides Lowe syndrome and often includes urine wasting of glucose, which is very rare in Lowe syndrome. In Lowe syndrome, the renal tubular dysfunction may be mild and involve only a few substances or may be severe and involve large losses of many substances and fluid.

The clinical signs of kidney abnormalities in Lowe syndrome are not present at birth, but usually become apparent by 1 year of age. Physicians who are not aware of this delay may be reluctant to diagnose Lowe syndrome during the first year, if the usual blood and urine tests of kidney function are normal. Many physicians may not be aware that the first sign of kidney tubular dysfunction in Lowe syndrome patients is urine wasting of small 'tubular' proteins, such as *retinol binding protein* or *N-acetyl glucosaminidase*. Wasting of these proteins can be diagnosed in the first few months of life, even before generalised amino acidurias (amino acids in the urine) or any other tubular dysfunction occurs. In an infant suspected to have Lowe syndrome, blood and urine screening tests for kidney abnormalities should be done every 3 months in the first year of life, every 6 months in the second year, and then at least yearly thereafter, until the full extent of the Fanconi syndrome becomes apparent.

#### *Treatment / Replacement therapy*

Some of the substances lost in the urine, such as organic acids and small tubular proteins, cause no clinical problem and do not need to be monitored or replaced. They are markers of tubular dysfunction and helpful in diagnosing Lowe syndrome. Loss of albumin in the urine may be large in some patients, but just reflects poor tubular reabsorption of normally-filtered albumin, so does not lower the blood albumin level or lead to the body swelling typical of clinical nephrotic syndrome.

On the other hand, some of the substances lost in the urine, like bicarbonate, sodium, potassium, phosphate and carnitine, are essential to normal body chemistry and need to be replaced. Excessive loss of these substances may result in serious metabolic problems, such as proximal renal tubular acidosis, hypokalemia, hypophosphatemia and carnitine deficiency (see *Kidney Function Blood Tests* and *Kidney Function Urine Tests below*). In addition, some patients may not make enough of the active form of 1,25-dihydroxy vitamin D (calcitriol), which is made in the kidney in normal proximal tubules.

Medications can be used to replace the lost substances and normalize the blood levels in most patients. These medications may include sodium bicarbonate or citrate, potassium citrate, potassium chloride, sodium phosphate, levocarnitine or calcitriol. The type of medication and dosage must be individualised for each patient by his physician. Blood and urine testing is done at intervals to monitor the benefits of therapy and to determine the appropriate doses of replacement medication. In addition, because the kidneys are often not able to conserve water and concentrate urine normally, a larger than normal intake of and free access to fluids is needed to prevent dehydration.

## *Kidney Function Blood Tests*

### **Serum Chemistries**

- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Total CO<sub>2</sub> or bicarbonate (HCO<sub>3</sub>) [test for acidosis]
- Calcium (Ca)
- Phosphorus (P)
- Magnesium (Mg)
- Uric acid
- Albumin, total protein
- Creatinine, blood urea nitrogen (BUN)

### **Tests for progressive kidney disease with anaemia**

- CBC: haemoglobin, haematocrit (FBC)
- Serum iron, ferritin, transferrin, T-saturation

### **Special blood tests**

- Amino acids (at diagnosis only)
- Total and free plasma carnitine

### **Bone-related serum tests**

- Calcium, phosphorus, alkaline phosphatase
- Parathyroid hormone (intact)
- Vitamin D-25-hydroxy, vitamin D-1,25-dihydroxy

## Urinalysis

- Protein (albumin)
- Glucose
- Blood
- Leukocyte esterase, nitrite
- pH (acidosis)
- Specific gravity (concentration)

## Random urine sample

- Amino acids (at diagnosis only)
- Tubular proteins: retinol binding protein, N-acetylglucosaminidase or lysozyme (at diagnosis only)
- Protein (or total protein)
- Calcium (Ca)
- Creatinine (Cr)
- Ratios: protein/Cr, Ca/Cr

## 24 hour urine collection

(not possible if bed wetter or not toilet trained)

- Total protein (protein electrophoresis not necessary)
- Creatinine and creatinine clearance
- For general stone evaluation — not Lowe syndrome specific:
- Calcium
- Citrate
- Oxalate (not needed; specific for another disease, primary hyperoxaluria)
- Uric acid (not needed, if kidney stone does not contain uric acid)

#### 4.4.2 Nephrocalcinosis / Nephrolithiasis

Nephrocalcinosis is a kidney disorder in which calcium and oxalate or phosphate are deposited in the kidney tubules and the areas in between them. This may result in impaired kidney function. Excessive loss of calcium in the urine can be part of the Fanconi syndrome and can be associated with kidney stones and deposits of calcium in the kidney tissue – nephrolithiasis. Patients with Lowe syndrome appear more likely to develop these conditions than other children with diseases associated with Fanconi syndrome. Extra citrate in the urine can combine with calcium to help keep the calcium in solution and prevent nephrocalcinosis and stones. Vitamin D therapy for treatment of rickets (see [Section 4.5.1. Rickets and Soft Bones](#)) should be carefully monitored in patients with Lowe syndrome to avoid worsening nephrocalcinosis. Calcium supplements should probably be avoided, unless blood calcium is low.

When nephrocalcinosis or nephrolithiasis occur, they may also cause microscopic amounts of blood to appear in the urine (haematuria). Nephrocalcinosis is best diagnosed by renal ultrasound and a plain abdominal X-ray. If a patient is suspected of having a kidney stone, a contrast X-ray study of the kidneys, like a CT scan (computed tomography) or intravenous pyelogram, may be needed to identify the exact position of any stones. A spot ‘urine calcium to creatinine ratio’ or a 24-hour urine calcium measurement may be needed to determine the extent of calcium wasting and its subsequent response to any therapy. The use of thiazide diuretics may be useful in some patients with nephrocalcinosis or stones.

#### 4.4.3 Kidney cysts

A few individuals with Lowe syndrome have reported kidney cysts, which are fluid-filled sacs that can arise anywhere within the kidney. Simple cysts, which are small, round, and homogenous, cause no harm. They occur frequently in normal individuals, even in young children. In older patients, complicated cysts (multiloculated, echogenic or calcified) may be cancerous, so need full evaluation with CT scans or possibly MRI. Simple cysts are usually just monitored with renal ultrasound.

#### 4.4.4 Kidney failure

Later in life, usually starting after the age of 10 years, the tiny filters of the kidney (glomeruli) may start to fail. In Lowe syndrome, kidney failure usually progresses slowly and is not complete until age 30 or 40 years. The exact cause of the filtration failure in Lowe syndrome is unknown, but is likely to be related to progressive injury to renal tubules leading to poor health and function of the attached glomeruli. Kidney failure is diagnosed when waste products, like creatinine and urea nitrogen, begin to accumulate in the blood instead of being filtered out. This may begin to happen even before any physical symptoms occur. Creatinine and urea nitrogen are made every day by normal body metabolism and are good markers for kidney filtration.

Creatinine is made by the muscles, so blood levels of creatinine may be lower than expected for a given degree of kidney failure if the muscle mass is decreased in Lowe syndrome. In that case, a 24-hour urine creatinine clearance gives a more accurate estimate of the kidney function than the blood creatinine alone. Symptoms of fatigue, decreased appetite, nausea and vomiting may occur when kidney function is less than 20% of normal, but these are often non-specific.

The degree of kidney failure, now referred to as chronic kidney disease or CKD, is classified into stages to help physicians better manage CKD. Symptoms of fatigue, decreased appetite, nausea and vomiting associated with kidney failure usually do not occur until CKD stage 5, when kidney function is less than 15% of normal, and serum creatinine is about 10 times normal (6-10 mg/dL). When patients reach CKD stage 4 and kidney function is between 15 and 30% of normal, physicians and families need to start thinking and planning for whether dialysis or transplant should be done when the patient reaches complete kidney failure, called end-stage kidney/renal disease (ESRD), which occurs in CKD stage 5. The quality of life on dialysis, whether the patient might be able to physically tolerate dialysis treatments, and whether comfort care might be the best option at ESRD should be carefully considered. Dialysis experience in Lowe syndrome is limited, but a few Lowe syndrome patients have been treated with chronic haemodialysis for several years, and at least one patient has done home peritoneal dialysis. Little is known about the success or long-term survival of kidney transplants in patients with Lowe syndrome.

#### *Other abnormal lab findings*

Patients with Lowe syndrome may have a variety of other abnormal laboratory findings, including high serum glutamic oxaloacetic transaminase (SGOT; also known as aspartate aminotransferase or AST), lactate dehydrogenase (LDH) and serum cholesterol levels, particularly high-density-lipoprotein cholesterol. AST and LDH are found in both liver and muscle. In most cases of Lowe syndrome, elevated serum AST (SGOT) and LDH result from impaired muscle integrity and are not related to liver problems. The reasons for elevation of serum cholesterol are not known, but might be related to factors other than Lowe syndrome.

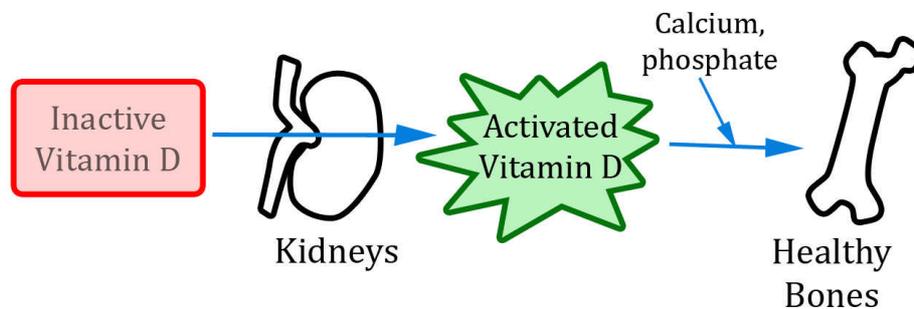
#### *Prognosis*

Although it is not possible to predict the future for any particular individual, some general observations can be made. With appropriate medical care, many of the problems associated with the syndrome can be treated effectively, allowing life expectancy to extend well into adulthood, with some young individuals living into their 40s and 50s. Progressive kidney failure appears to present a significant limitation on life span. However, deaths from complications of Lowe syndrome have occurred at all ages due to infection, dehydration and pneumonia which can lead to organ failure and subsequently to death. These conclusions rely on current medical practice and may change significantly with more research and the advancement of new treatments.

## 4.5 Bones and joints

### 4.5.1 Rickets and soft bones

Many children with Lowe syndrome have a history of soft bones or rickets. This condition probably results from a combination of problems. As bones grow and form they need to "ossify" or become solid. Phosphate, calcium, vitamin D, other nutrients and hormones, and proper acid-base balance, are needed for proper ossification and bone remodelling with growth. Vitamin D is normally converted to its active metabolite, 1,25-dihydroxy vitamin D or calcitriol, in the kidney tubules.



Since the kidney tubules are abnormal in Lowe syndrome, some patients may not make enough calcitriol to keep the bones strong and to enhance intestinal absorption of phosphate supplements. In addition, muscle tension on the bones due to exercise and movement is also thought to be necessary to keep the bones strong. When the muscles are weak (hypotonia), they do not perform this function well. Low blood phosphate, acidosis (from renal Fanconi syndrome), hypotonia and kidney problems in Lowe syndrome all place the boys at risk of developing soft bones, rickets (in the growing child) or osteomalacia (in the adult). Problems associated with these conditions include fractures and scoliosis.

Rickets or osteomalacia can often be improved by giving vitamin D with oral preparations of neutral phosphate, as well as alkali salts like sodium and potassium bicarbonate to help correct the electrolyte losses due to the Fanconi syndrome. A side effect of oral phosphate is loose stools, so the dosage must be started low and carefully monitored. Occasionally, vitamin D metabolite preparations, such as calcitriol or dihydrotachysterol, are needed. Therapy with these medications should be carefully monitored to prevent the complications of kidney stones or calcium deposits in the kidney tissue (see [Section 3.4.2 Nephrocalcinosis](#)). Since patients with Lowe syndrome may be predisposed to developing kidney calcifications even without vitamin D metabolite therapy, the kidneys should be checked for this condition by ultrasound or on X-ray before starting and at intervals during any therapy with vitamin D metabolites. Plain vitamin D (parent compound) may not be an effective therapy because it may not be converted by the kidneys to the active metabolite.

All medications and dosages must be individualised for each child by his doctor. Blood and urine tests and X-rays are usually ordered periodically. Blood tests may be done to measure calcium, phosphorus, bicarbonate, alkaline phosphatase, vitamin D metabolites and parathyroid hormone:

**Alkaline phosphatase** is an enzyme made in bone. When bone is being actively broken down, as in rickets, or when bone is actively growing and forming new bone as during healing of rickets, the blood level of alkaline phosphatase will be elevated.

The **metabolites of vitamin D** that are measured are 25-hydroxy vitamin D, which is made in the liver, and 1,25-dihydroxy vitamin D or calcitriol, which is made in the kidney. The 25-hydroxy vitamin D level indicates whether the dietary intake of vitamin D is adequate, while the calcitriol level indicates whether the kidney is making adequate amounts for bone growth and prevention of rickets.

**Parathyroid hormone** is a hormone made in glands in the neck near the thyroid. Parathyroid hormone regulates calcium levels in the body and may be elevated when a patient has rickets or is receiving too much phosphorus supplementation.

**Urine tests** may be done to measure phosphorus, calcium, albumin, creatinine and pH, and will indicate the severity of the urinary losses of calcium, phosphorus, albumin and bicarbonate.

Changes for all medications should be made only by the doctor, since medical problems may develop if medication doses are too high or too low.

### 4.5.2 Fractures

Around half of boys with Lowe syndrome will suffer from bone fractures, usually as a result of reduced bone density, also known as osteopenia/osteoporosis, due to the same abnormalities in vitamin D and calcium metabolism that cause rickets. As with rickets, hypotonia may lead to weakened bones that are more susceptible to break.

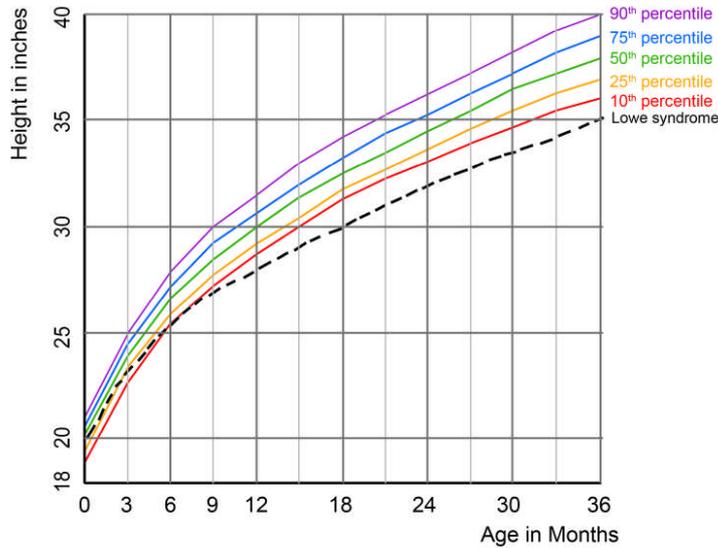
These fractures often involve the bones in the upper leg at about 6 years of age when they learn to walk. Roughly 50% of the boys reporting a fracture have multiple fractures, usually in the legs, arms, hands, fingers and/or wrists.

Early diagnosis and treatment of metabolic imbalances such as hypophosphatemia, acidosis, vitamin D deficiency and low bone density (osteopenia/osteoporosis), as well as regular physical exercise and weight bearing activity, could help increase bone strength and reduce the likelihood of breakages.

### 4.5.3 Short stature

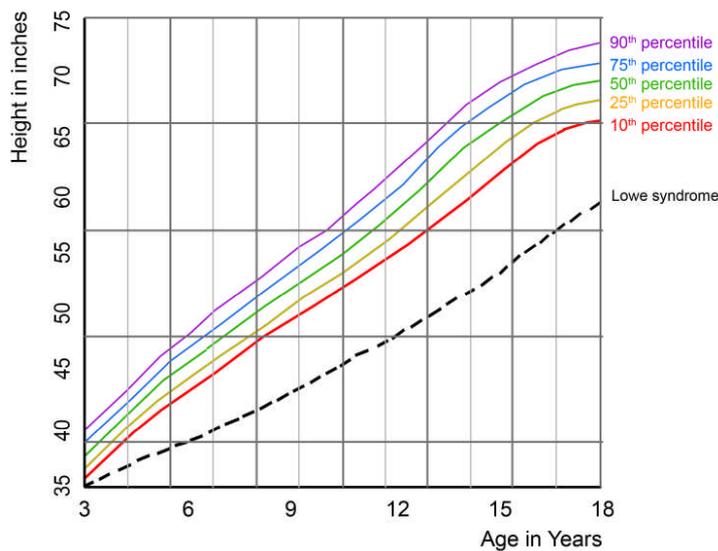
At birth, boys with Lowe syndrome are usually of normal length. However, by their first birthday, most have fallen well below the 10<sup>th</sup> percentile (see graphs below). While the boys continue to grow they do so more slowly than normal, achieving an average adult height of around 5 feet (150 cm). However, as yet the underlying cause of short stature has not been defined.

### Height growth chart 0-36 months



The coloured lines represent normal growth patterns for boys ages 0-36 months. The black, dashed line represents the average growth pattern of boys with Lowe syndrome ages 0-3 (based on data from the *Lowe Syndrome Comprehensive Survey, 1991*).

### Height growth chart 3-18 years



The coloured lines represent normal growth patterns for boys ages 3-18 years old. The black, dashed line represents the average growth pattern of boys with Lowe syndrome ages 3-18 (based on data from the *Lowe Syndrome Comprehensive Survey, 1991*).

#### 4.5.4 Growth hormone

There are a number of reports regarding treatment of boys with Lowe syndrome using human growth hormone (HGH) therapy, helping them to achieve heights within the normal range and improving bone density. HGH can act by stimulating cell growth and multiplication.

However, more studies are required in order to determine its safety and effectiveness. The potential benefits of this therapy need to be weighed against its high cost and the potential social and psychological impact it may have.

### 4.5.5 Scoliosis

Between adolescence and adulthood, approximately half of boys with Lowe syndrome develop curvature of the spine, also known as scoliosis. Cases can vary from mild, which may be treated using a brace or with surgery, to severe, where it significantly affects mobility, causes back pain and reduces lung capacity.

### 4.5.6 Kyphosis

Some Lowe syndrome patients also suffer from kyphosis, an abnormally rounded upper back, or 'hunchback'. This may be caused by osteoporosis resulting in compression fractures of the vertebrae, developmental problems, degenerative diseases like arthritis, or trauma. Kyphosis can be treated using physical therapy, body braces, for example the Milwaukee brace (CTLSO), and sometimes by surgery.

### 4.5.7 Plantar fasciitis

Plantar fasciitis is a painful inflammation of the plantar fascia, a fibrous band of tissue that extends along the sole of the foot. The pain is usually felt on the underside the heel and is most intense during the first steps of the day. There are a range of treatment options available, including rest, stretching exercises, wearing shoes with good support, massage, heat/cold therapy, orthotics, anti-inflammatory medications and even surgery.

### 4.5.8 Palmar fibromatosis

Palmar fibromatosis, also known as Dupuytren's disease, refers to the growth of fibrous, tumour-like nodules (fibromas) in the connective tissues of the hand leading to tightening of tissue under the palm of the hand, causing the fingers to bend. This has been noted in a number of Lowe syndrome boys, but currently there is no known effective treatment. Fibromatosis can also occur in the soles or arches of the feet. In contrast to desmoid tumours (see [Section 4.5.9](#) below) which are more invasive, fibromas tend to be benign and remain in one region.

### 4.5.9 Desmoid tumours

Some Lowe patients suffer from desmoid tumours that develop in fibrous connective tissues throughout the body and are scar-like in appearance. While desmoid tumours are not considered cancerous as they generally do not spread to other parts of the body, they can aggressively invade surrounding tissues and are difficult to control. While desmoid tumours may be treated by surgery, even following apparent complete removal, due to their invasiveness into other tissues they often recur.

#### 4.5.10 Joint swelling and arthritis

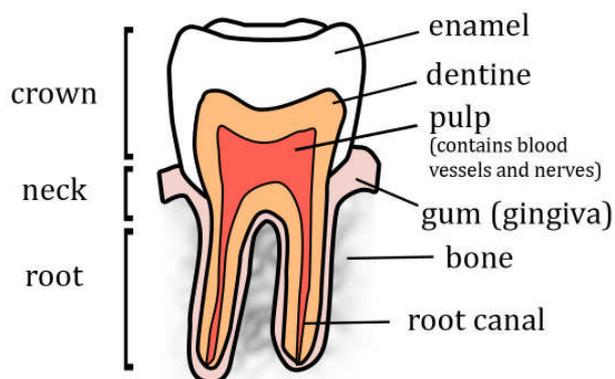
Joint swelling and arthritis are also associated with Lowe syndrome, and are especially prevalent in teenage and adult life. Commonly affected areas include neck, shoulders, elbows, wrists and fingers, hips, knees, ankles and feet/toes. The exact cause of joint swelling and arthritis in Lowe syndrome is not fully understood and the only treatment is supportive therapy for the pain, including physical therapy, regular exercise and massage.

#### 4.5.11 Wheelchairs and mobility devices

Due to the range in severity of bone-related disorders in Lowe syndrome, there is a wide range of mobility requirements. Some Lowe syndrome patients are very mobile, whereas others require a wheelchair or walking device - some from infancy, some only later in life and some only occasionally.

### 4.6 Teeth and gums

Lowe syndrome individuals suffer from a range of dental problems and may require extensive dental care. These include: teeth crowding, misalignment and delayed shedding of primary teeth, which may be caused by high narrow palate, small mouth, rickets, poor tongue posture, low oral muscle tone and a double row of teeth. In addition, other metabolic factors may result in susceptibility to decay, teeth yellowing due to metabolic imbalance resulting from renal problems, tartar formation or filling of the root canal space by dentin.



Regular dental check-ups should begin following the eruption of the first baby teeth. It is important to note that for individuals with Lowe syndrome behaviour management can play a significant role in attending dental appointments.

#### 4.6.1 General anaesthetics

Individuals with Lowe syndrome often require a general anaesthetic for dental procedures such as examinations, x-rays and cleaning, as the boys usually resist treatment. With increased age and maturity some individuals no longer need general anaesthesia for dental procedures.

### **4.6.2 Extractions**

In individuals with Lowe syndrome, primary or 'baby' teeth are extracted most often, however, sometimes permanent teeth also require extraction. Reasons for tooth removal include: infection/decay, loose teeth, overcrowding, misalignment/obstructing other teeth.

### **4.6.3 Dental surgery**

Many individuals with Lowe syndrome require dental surgery for a variety of problems, including: cavity filling, application of enamel coating, crowns, tooth removal (primary, permanent and wisdom), dental implants, periodontal work, gum removal and surgery for double row of teeth.

### **4.6.4 Braces and orthodontic devices**

Braces and other orthotic devices are successful in a small number of individuals with Lowe syndrome, and have been used to treat high palate, overcrowding and misalignment of teeth. Success is mainly determined by the temperament and behaviour of the individual as it requires tolerating numerous procedures involved in the placing and wearing of such orthotic devices.

### **4.6.5 Gum problems**

Many individuals with Lowe syndrome experience gum problems, in particular gingivitis and periodontitis. Gingivitis occurs when the gums become inflamed due to the build-up of bacterial plaque in the mouth. When left uncontrolled, gingivitis can progress to periodontitis, where plaque bacterial lesions lead to destruction of the bone and ligaments that hold teeth in place, causing loosening of the root, drifting and eventually tooth loss. In Lowe syndrome, a number of other factors also play a role in gum problems, including metabolic imbalances, medication, poor oral hygiene, breathing only through the mouth and gums that are swollen for no apparent reason.

### **4.6.6 Dental Cysts**

Individuals with Lowe syndrome may experience dental cysts, which are quite common with teething but often resolve once the permanent teeth are established. Dental cysts are fluid- or soft material-filled sacs that form around the teeth and may become infected (abscess), weaken the jaw, press against teeth and affect the normal function of the teeth and mouth.

Dental cysts can independently resolve especially after teething, but others may need treatment by a dentist or dental surgeon.

## 4.7 Blood and urine tests

### 4.7.1 Blood tests results

Example Blood Lab Test Results				
Test	LAB RESULTS		Units	Expected Range
	Out of Range	Within Range		
<b>Comprehensive Metabolic Panel</b>				MAIN
GLUCOSE		77	MG/DL	65-100
BUN		19	MG/DL	8-25
CREATININE		0.7	MG/DL	0.6-1.3
EGFR AFRICAN AMER.		102	ML/MIN/1.73	>60
EGFR NON-AFRICAN AMER.		85	ML/MIN/1.73	>60
CALCULATED BUN/CREAT		27		6-28
SODIUM		138	MEQ/L	133-146
POTASSIUM		3.9	MEQ/L	3.5-5.3
CHLORIDE		102	MEQ/L	97-110
CARBON DIOXIDE		25	MEQ/L	18-30
CALCIUM		9.8	MG/DL	8.5-10.5
PROTEIN, TOTAL		7.3	G/DL	6.0-8.4
ALBUMIN		4.7	G/DL	2.9-5.0
CALCULATED GLOBULIN		2.6	G/DL	2.0-3.8
CALCULATED A/G RATIO		1.8		0.9-2.5
BILIRUBIN, TOTAL		0.6	MG/DL	0.1-1.3
ALKALINE PHOSPHATASE		42	U/L	30-132
SGOT (AST)		34	U/L	5-35
SGPT (ALT)		25	U/L	7-56
<b>LIPID PANEL</b>				MAIN
CHOLESTEROL		196	MG/DL	<200
TRIGLYCERIDES	179		MG/DL	<150
HDL CHOLESTEROL		89	MG/DL	>39
CALCULATED LDL CHOL		71	MG/DL	<100
RISK RATIO LDL/HDL		0.80	RATIO	<3.22
<b>CBC (COMPLETE BLOOD COUNT)</b>				MAIN
WBC	3.8		K/UL	4.0-11.0
RBC		4.04	M/UL	3.80-5.10
HEMOGLOBIN		13.2	G/DL	11.5-15.5
HEMATOCRIT		40.8	%	34.0-45.0
MCV	101.0		fL	80-100
MCH		32.7	PG	27.0-34.0
MCHC		32.4	G/DL	32.0-35.5
RDW		12.2	%	11.0-15.0
NEUTROPHILS		40	%	40-74
LYMPHOCYTES		39	%	19-48
MONOCYTES		15	%	4-13
EOSINOPHILS		6	%	0-7
BASOPHILS		0	%	0-2

This column will show all test scores that are in an **unacceptable range**. You should contact Family Physician or internist to discuss these results.

This column notes your actual test score. The face that your score is in this column means your test score is within **normal range**.

This column gives you the minimum and maximum of an acceptable test score. As long as your results fall between these two numbers your results are considered normal.

The following is a brief explanation of the various studies performed on the full blood count. **THIS SHOULD NOT BE USED FOR DIAGNOSIS OF DISEASES WITHOUT A PHYSICAL EXAMINATION BY A PHYSICIAN AND COMPLETE MEDICAL HISTORY.**

### ***Comprehensive metabolic panel***

**Glucose** - Shows how well the body handles carbohydrate metabolism. Glucose may be burned directly or stored as fat. The primary source of glucose is through conversion of the glycogen stored in the liver. Decreased sugar levels (hypoglycaemia) can be caused by pancreatic disorders and excess insulin.

Higher sugar in the urine may mean that food sugar is not being used normally, a warning sign of diabetes or possibly other diseases (like Renal Fanconi syndrome, which can be part of Lowe syndrome).

**Urea** - Urea is used to assess kidney function, and is the end product of protein metabolism. Urea is the main waste product produced by the liver during breakdown of protein. Elevated urea levels are found in urinary tract obstruction, congestive heart failure, gastrointestinal bleeding, and in individuals on a high protein diet. Antibiotics and a number of drugs can increase levels as can stress, gout, internal bleeding and ulcers. It varies with dietary protein intake. Low levels may be caused by malnutrition, liver failure and increased pituitary activity. Diets low in protein and high in carbohydrates can also be responsible for low urea levels.

**Creatinine** - Creatinine is the breakdown product of creatine, which is used for skeletal muscle contraction. Excreted entirely by the kidneys, presence may suggest a kidney problem.

**Sodium** - Sodium content of the blood is a balance between sodium intake and kidney excretion. Therefore, water and sodium are physiologically interrelated. Increased levels found may indicate endocrine disorders, dehydration, steroid drugs and others. Kidney and heart disease can be due to various causes such as diarrhoea, cirrhosis, kidney problems, etc.

**Potassium** - Potassium is a major ion within the cell. Maintains balance of fluids in cells and helps carry out enzyme reactions. Highly elevated levels, secondary to kidney failure or liver disease, can lead to heart failure. Decreased levels can be caused by diabetes, vomiting and diarrhoea. Blood potassium levels depend on many factors including:

- **Aldosterone** - (this hormone tends to increase the kidney losses of potassium.)
- **Sodium reabsorption** - (as sodium is reabsorbed, potassium is lost.)
- **Acid-base balance** - (acidotic states tend to raise the blood potassium levels.)

**Chloride** - A salt of hydrochloric acid. Along with bicarbonates, potassium, and sodium, chloride helps control the body's acid-base system and control water metabolism. Elevated with kidney disease, dehydration, aspirin toxicity; decreased with vomiting, diarrhoea, heart disease and diabetes.

**Carbon dioxide** - In normal breathing, CO<sub>2</sub> is eliminated through the lungs. Increased primarily by conditions like emphysema and asthma where sufficient CO<sub>2</sub> is not exhaled, it can also be increased with metabolic alkalosis caused by diuretic drugs, antacids and steroid hormones. CO<sub>2</sub> is decreased with metabolic acidosis caused by drug poisoning (especially aspirin), diarrhoea, liver and kidney diseases.

**Calcium** - Calcium is a mineral important for bone formation, muscle contraction and blood clotting. In addition, calcium is involved with maintaining the stability of nerve cells. Calcium levels in blood are strictly controlled by various substances called hormones. Abnormal blood calcium levels may be the results of excessive vitamin D, antacids, magnesium, etc. Low values could mean malabsorption/diarrhoea, renal or digestive problems.

**Total protein** - Special combination of amino acids whose balance is important for cell growth and repair. Total protein is one way to assess liver function. More important, the measure of total protein is a measure of albumin, one of the proteins synthesised by the liver. When disease affects the liver cells, the cells lose their ability to make albumin. Therefore, the measure of total protein is a rather indirect and inadequate indication of liver function. Measuring the level of albumin is much more reliable.

**Albumin** - Albumin is the major protein of the blood. Presence in urine is often a sign of kidney disease. Decrease often indicates liver damage. Albumin levels are also used as an indication of general health and nutritional status.

**Globulin** - A simple protein found in the blood. Includes alpha, beta and gamma globulin. Some globulins function as antibodies, others are responsible for the transport of lipids, iron and copper in the blood. Abnormal values could reflect a liver problem, such as cirrhosis, mononucleosis or cancer.

**A/G ratio** - The Albumin Globulin Ratio is another indicator of liver function since the presence of these two proteins in the blood should be constant.

**Total bilirubin** - A gold coloured pigment and body waste product. It is formed by the spleen from the haemoglobin in blood cells when they break down. Increased total bilirubin is associated with cirrhosis, gallstones, or cancer of the pancreas.

**Alkaline phosphatase** - An enzyme found in almost all tissue of the body. Highest levels are found in the intestine, kidney, bone and placenta. The enzyme form present in serum comes from the liver and bone. Therefore, measurements of serum alkaline phosphatase are particularly useful in the evaluation of liver and bone diseases. Minor increases in the level of alkaline phosphatase are sometimes observed during the normal aging process.

**AST (SGOT)** - The enzyme SGOT is found in very high concentration in the heart and in the liver and in moderately large amounts in the skeletal muscle, kidneys and pancreas. A characteristic rise in SGOT level occurs in more than 95% of patients with proven myocardial infarctions.

**ALT (SGPT)** - An enzyme that speeds up chemical organic reactions that occur within cells.

## **CBC (Complete Blood Count)**

**WBC** - White blood count - Part of the immune system. Fights infection.

**RBC** – Red blood count. Determines the number of red blood cells in one cubic meter of blood. MCV, MCH, and MCHC are indices that help diagnose the cause of anaemia.

**Haemoglobin** - Iron-containing protein in red blood cells that carries oxygen from lungs to tissues. Haemoglobin level is a good index of the blood's oxygen carrying capacity.

**Haematocrit** - Part of the blood that is in the red blood cells. Excessive amounts may be due to insufficient oxygen, carbon monoxide, or chronic lung disease. Decreased levels may mean anaemia.

**MCV** - Average of red blood cell volume. Indicates whether cells are of normal size.

**MCH** - The weight of haemoglobin in an average red blood cell.

**MCHC** - The amount of haemoglobin in an average cell.

**RDW** - Red cell distribution width (RDW) is a calculation of the variation in the size of your RBCs. In some anaemias, such as pernicious anaemia, the amount of variation (anisocytosis) in RBC size (along with variation in shape – poikilocytosis) causes an increase in the RDW.

**Neutrophils** - Primary cells that destroy microorganisms and toxic/disease causing substances.

**Lymphocytes** - Cells that represent antibody activity in producing immunity to disease.

**Monocytes** - These cells are old lymphocytes and typically represent the body's chronic disease processes.

**Eosinophils** - Ratio is related to allergies and parasitic infections.

**Basophils** - Only 1% of corpuscular volume. Function not understood.

**Platelet count** - A protoplasmic disk, smaller than a red blood cell, necessary for coagulation.

**LDH** - An enzyme which is found in human tissues, especially the heart, kidneys, liver and muscle. Elevated in a number of diseases and drug reactions.

**Phosphate** - Necessary for many body functions and directly related to calcium metabolism. Hyperphosphatemia (high levels of serum phosphorus) can be caused by hypoparathyroidism, kidney failure or increased dietary intake. Hypophosphatemia (low levels of phosphorus) can be caused by inadequate dietary intake, vitamin deficiency, alcoholism, chronic antacid ingestion and hyperthyroidism. Symptoms may include retarded skeletal growth in children, anorexia, dizziness and muscle weakness.

**Uric acid** - Uric acid is an end product of the body's metabolism and is formed mainly by the liver during the breakdown of nucleic acids. Following handling by the

kidney, it is excreted in the urine. High levels might indicate gout, arthritic condition, or kidney problems. Amounts can vary with certain diseases and diets overly rich in some types of fish and gland foods. High levels can be considered a high risk factor, particularly if accompanied with high triglyceride and low HDL.

**Cholesterol** - The cholesterol (solid alcohol, not a true fat) in our bodies is carried around and attaches to five major fat particles that are called lipoprotein.

**Triglycerides** - A true fat and heart risk factor. This is an important lipid component which takes the available cholesterol and makes it "stick" to the artery walls causing fat deposit build up. High triglycerides are generally caused by high dietary intake of carbohydrates, alcohol, sugars and yeast breads, and are best treated with a low-carbohydrate diet.

**HDL (Good cholesterol)** - A lipoprotein that accepts free cholesterol from the tissue for transport to the liver. HDL helps remove lipids (fats) from artery tissues and also protects plasma LDL from damaging the artery, thus limiting plaque build up.

**LDL (Bad cholesterol)** - Elevated levels of LDL are strongly associated with heart disease. The LDL typically contains 60-70% of the total serum cholesterol and therefore its concentration closely correlates with the concentration of total cholesterol.

**LDL/HDL ratio** - A ratio of total cholesterol divided by the High Density lipids (HDL) establishes this important heart risk factor.

**T3 uptake** - one of two iodine-containing hormones produced by the thyroid gland.

**T4** - Thyroxine, the other iodine-containing hormone produced by the thyroid gland.

**T7 calculation** - Calculated by multiplying the  $T4 \times T3$ . Excessive values may mean hyperthyroidism. Lower values may indicate hypothyroidism.

**Urea/Creatinine ratio** - The daily production of creatine, and subsequently creatinine depends upon muscle mass, which fluctuates very little. With normal kidney excretory function, the serum creatinine level should remain constant and normal in adults. Therefore only kidney disorders (as mentioned before) will cause an abnormal elevation of creatinine. The normal Urea/Creatinine ratio is 20:1.

**GGT** - Enzyme primarily in heart and liver. Released in blood when there is heart muscle damage, liver cell damage or some parasitical or bacterial infections. Also elevated with pancreatitis, infections, mononucleosis and certain muscle diseases.

**Iron** - Iron is required to transport oxygen from the lungs to body tissues. Abnormal levels of iron are characteristic of many diseases, including iron deficiency anaemia. Most iron in the body is in the haemoglobin of red blood cells. Iron deficiency anaemia has many causes, including: insufficient iron intake, inadequate absorption in the intestines, increased requirements of iron (as in growing children) and loss of blood (as in excessive menstruation, bleeding peptic ulcer or colon cancer).

Because serum iron levels may vary during the day, specimens should be drawn in the morning, especially when the results are used to monitor iron replacement therapy.

### 4.7.2 Platelet defect in Lowe syndrome

Joel Lunardi in France highlighted a platelet defect which may affect Lowe children. This can be problematic in bleeding, especially during certain types of surgery.

To determine whether your child might be at risk, a PFA100 platelet screening test should be organised at your local hospital. It is quick and easy although about 20mls of blood is taken which might be a little bit of a problem with babies or younger children. We are interested to find out whether this platelet problem exists with all Lowe children/adults or just some and so your results would be very interesting.

### 4.7.3 Urinalysis (analysis of urine)

**Colour** – Unusual colour due to medications, foods, bacteria

**Appearance** – Clear or slightly hazy

**Specific Gravity** – The density of the urine. Greater could be excessive sugar or protein, lower could be excessive fluid intake or kidney disease.

**Leukocyte Esterase** – Positive may indicate urinary infection, large doses of Vitamin C or antibiotics.

**Nitrite** – Positive may indicate urinary infection, large doses of Vitamin C or medications.

**pH** – Measures acidity or alkalinity. The pH reflects the type of foods eaten and the functioning of lungs, kidneys and metabolism.

**Protein** – Under normal conditions, protein is not extracted in the urine.

**Glucose** – Sugar level. Excessive due to medication, diabetes or Fanconi syndrome such as Lowe syndrome.

**Ketone** – Waste products of fat breakdown. Measured in blood or urine. Greater than normal may indicate diabetes, starvation, low-carbohydrates, diarrhoea, severe stress or too long fasting.

**Urobilinogen** – Can determine whether jaundice is caused by liver disease, obstruction of bile ducts, and destruction of red blood cells.

**Bilirubin** – Indicates liver disease often before symptoms appear.

**Occult Blood** – Presence of blood cells in urine.

## 4.8 General health concerns

As well as the specific medical issues discussed above, Lowe syndrome can often give rise to more general health concerns.

### 4.8.1 Metabolic imbalance

Normal daily levels of fluid intake and medications are important to maintain metabolic balance in children with Lowe syndrome, and anything that interferes with this may increase their risk of metabolic imbalance. This often happens as a result of sicknesses, such as colds or flu, vomiting or diarrhoea and may also occur when uncontrolled seizures prevent normal fluid intake. In such cases parents/carers must seek rapid medical attention as it may be that medicines and intravenous (iv) fluid administration may be required.

In addition, some Lowe children may require iv fluids and medications during anaesthesia, surgery or other procedures that include periods with no eating or drinking, in order to prevent metabolic imbalance.

### 4.8.2 Constipation

50% of individuals with Lowe syndrome suffer from constipation. While dehydration and poor muscle tone contribute to constipation, some healthcare professionals believe this may represent a specific feature of Lowe syndrome, and that there is a direct effect of the mutant *OCRL1* gene product on intestinal muscles, preventing effective movement of the stool along the intestine.

Treatment for constipation includes adequate hydration by drinking lots of water, and plenty of dietary fibre. However, medication may be required if this is not effective, but should only be applied under the supervision of a doctor. Importantly, *enemas are not recommended* as they may lead to significant, potentially life-threatening metabolic imbalance.

### 4.8.2 Respiratory problems

Due to hypotonia (see [Section 4.3.5 Hypotonia](#)) boys with Lowe syndrome are less able to cough strongly and effectively, and so may be more susceptible to developing bronchitis, pneumonia and other respiratory infections. During episodes of respiratory illness, individuals with Lowe syndrome should be carefully monitored, and parents/carers should learn how to administer postural drainage and percussion therapy, which may help loosen mucous and other lung secretions so that they can be effectively drained.

### 4.8.3 Eating difficulties

Hypotonia can also affect the ability of Lowe individuals to suck and swallow, which may result in inadequate intake of food and drink, and an inability to take oral medications. Poorly coordinated swallowing can also increase the risk of individuals developing aspiration pneumonia, where food or fluid goes down the windpipe into the lungs rather than down the oesophagus to the stomach, leading to inflammation

and/or infection. Help to improve the ability to suck and swallow by feeding training may be available from occupational, speech and language therapists.

When a child is unable to take in daily food and drink effectively, there are a number of alternative feeding methods:

- **Nasogastric (NG) tube.** This is a plastic tube which is inserted through the mouth or nose down into the stomach. It is non-permanent.
- **Gastrostomy tube (PEG tube, G-tube or button).** This is a plastic tube surgically inserted through the abdominal wall directly into the stomach. It is a long-term/permanent solution.

Another common digestion problem associated with Lowe syndrome is gastro-oesophageal reflux disease (GORD). In this condition, due to hypotonia, the muscle at the top opening of the stomach does not shut tightly, leading to food and stomach acids coming back up the oesophagus. This can result in acid indigestion (heartburn), vomiting and inflammation of the oesophagus, as well as increasing the risk of aspiration pneumonia. Diagnosis of GORD requires imaging examination of the upper gastrointestinal tract and a scintiscan (X-ray imaging with a radioisotope tracer) to detect reflux. Treatment options include medication to reduce stomach acid and surgery, as well as lifestyle adaptations, such as eating upright and elevating the head end of the bed to reduce acid going up the oesophagus.

#### 4.8.5 Cysts

Cysts are a common problem in Lowe syndrome and occur in a number of different places, including the skin, mouth (see [Section 4.6.6 Dental cysts](#)), kidneys and even brain. Dental cysts may appear at teething, but as boys grow older, kidney and skin cysts are observed more frequently. Increasingly into adulthood, cysts develop in the skin of the buttocks and lower back, becoming painful and sometimes infected. Scans have also shown the presence of cysts in the brains of Lowe individuals, but it is currently not understood exactly what the effects of these are. The cause of these cysts in Lowe syndrome is not known, but is likely linked to the disrupted enzyme function. Therapy with retinoic acid derivatives is an option, but the potential negative effect of this treatment upon kidney function is unclear at present, so caution should be taken.

#### 4.8.6 Undescended testes

Failure of the testicles to descend into the scrotum, also known as cryptorchidism, is present in around 30% of Lowe individuals at birth. Of these, roughly a third will undergo natural descent of the testes over time, but the remaining two thirds should be assessed before they are 2 years old to investigate whether medical therapy or surgical correction are required.

### 4.8.7 Delayed puberty

In some cases of Lowe syndrome puberty is delayed and some boys will need hormonal stimulation. The timing of this needs to be right and should be discussed with an endocrinologist well in advance.

As with part of a normal education, boys with Lowe syndrome should learn about the anatomy of male and female bodies, sex education, reproduction and methods of contraception. However, in some cases it may not be appropriate to give too much information, and it is up to parents to decide what level of detail their child will be able to cope with. All children need to understand when private acts, such as being naked and undressing, are appropriate and inappropriate. Often children with learning disabilities struggle to understand simple verbal explanations of what is expected of them in each situation, and may benefit from visual cues to help them. For example, a picture of a fully-dressed child could be used to symbolise when wearing clothes is appropriate, whereas, a picture of a closed bathroom door, could be used to indicate that the bathroom is a private place. Social stories are another tool that may be used effectively to teach children the differences between private and public behaviours. It is important to emphasize that the behaviours of children with developmental problems should not be seen as being 'good' or 'bad', but more that there are certain behaviours that are *expected* of every child. In particular, young individuals may sometimes need specific guidance about when and where it is appropriate to masturbate.

Understanding the difference between public and private is also vital to help children understand which parts of the body it is acceptable for others to touch. As boys with Lowe syndrome are friendly, trusting and like to please, they're potentially at risk for physical and sexual abuse. As such it may be necessary to teach adolescent boys about when touching is appropriate or inappropriate ('good touch' and 'bad touch').

## 4.8 Prognosis

It isn't possible to accurately predict the medical future of particular individuals with Lowe syndrome, but we can make some general predictions. With appropriate medication and supportive care, many of the associated symptoms can now be effectively treated, meaning that the life expectancy of some young men may extend into their 30s or 40s. One significant limitation on life span is the development of chronic kidney disease (see [Section 4.4.4 - Kidney failure](#)). In addition, deaths due to dehydration, infection and pneumonia can occur at any age.

However, further research and the development of new treatments may improve medical practice and significantly improve prognosis and life span in the future.



# 5. Development and Education

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## 5.1 Introduction

This section looks at the development and educational needs of boys with Lowe syndrome. This does not pretend to be a comprehensive guide; children and families are all different, needs vary and, sadly, educational provision varies from area to area. This section gives an idea of the 'toolkit' of professionals that children are likely to need and some key areas that will need consideration.

Lowe syndrome boys show a wide spectrum of symptoms which can vary greatly, even between males in the same family carrying identical mutations. While the severity of symptoms and age of achievement of major developmental milestones varies, there are some general observations that can be made regarding developmental and educational needs.

Due to the physical and mental effects of Lowe syndrome, affected boys are typically significantly delayed in many aspects of development, although their development does generally pursue a normal sequence. Development can be much further ahead in one particular area (eg language) compared to other areas (eg motor skills). In order to help Lowe syndrome boys achieve their full potential, there are a growing number of educational schemes and therapies that have been developed.

Boys with Lowe syndrome have bubbly personalities, even those who suffer behavioural problems - they're kind and sociable with a great sense of humour and often with a love for music. In the context of a stimulating and nurturing environment where they are welcomed and appreciated as unique individuals, Lowe syndrome boys can flourish and become well integrated into family life and be functioning members of the community.

## 5.2 Infancy

### 5.2.1 Early intervention

Early intervention in the form of support and service provision has been scientifically shown to improve the developmental progress of disabled children. If early intervention measures involving both the child and their family are taken as soon as the need becomes apparent, the development of a child can progress significantly faster than if it is left unaddressed until age 6+.

A crucial role in development and education is played by parents, and they should find out everything about the programs available to help their child's development.

### 5.2.2 Physical development

Physiotherapy is of great benefit to boys with Lowe syndrome. Depending upon your location and local services, there may be access to local infant intervention physiotherapy, or if not, this may be arranged through private healthcare. Parents can often be trained by healthcare professionals to undertake physiotherapy in their own homes.

Physical development in affected boys is generally delayed, and initial physiotherapy will involve helping the boys to hold up their head when in a prone position, roll over, sit unaided and eventually crawl – the majority of boys will reach these milestones from a few months up to five years of age.

### 5.2.3 Speech development

Lowe syndrome boys usually have delayed speech development, which is especially frustrating for parents. The majority of boys will eventually learn to talk: most can

imitate words by age 2½, and by 7 nearly all can talk to some extent, able at the very least to make a phrase by combining two or more words. Indeed, Lowe syndrome boys are often extremely talkative!

A number of factors are involved in the delay in speech development, including physical causes (eg hypotonia, poor eyesight, high arched palate), general learning difficulties (eg in understanding words, processing and organising information, and effective communication) and environmental factors (eg limited learning, few social activities, and inability to move around independently).

### 5.2.4 Eating problems

Sometimes, the causes of delayed speech can also lead to problems in eating. For example, hypotonia can result in a reduced ability to control movement of the lips, tongue and jaws making actions such as sucking, chewing and swallowing much more difficult. Consequently, some boys find adjusting from baby food to adult food tricky. In these cases speech and language therapists should be consulted, and an oral-motor treatment plan can be included in their therapy. Most Lowe children can eat adult table food by age 5.

## 5.3 Middle childhood and adolescence

### 5.3.1 Walking

In most cases, physical therapy is still required into middle childhood, where the emphasis shifts to more physically demanding and complicated activities (gross motor skills), such as walking. Walking can be either slightly or significantly delayed in Lowe syndrome: some boys learn to walk before they are 2, and around half can walk alone by the age of 4. By 7, most boys can walk, and almost all are able to by 11 years old.

### 5.3.2 Toileting and self-help skills

Toilet training boys with Lowe syndrome can be challenging, especially night-time training. While some boys do succeed at a young age, most will begin training early but only achieve this goal between 5-13 years of age, and some not until even older. Half of Lowe syndrome boys suffer from constipation (see *Section 3.8.2*), which can further complicate toilet training. For support and advice about toilet training try contacting the NHS incontinence team.

Dressing and grooming themselves are among other self-help skills which are often delayed in Lowe syndrome. Actions that require more careful coordination (fine motor skills), such as writing, doing up buttons or zips and tying shoelaces can be very difficult to achieve. In some cases modifications to clothing, such as using velcro

fastenings on shoes and clothes, elastic waistbands, no heel socks and pullover shirts can help give children more achievable self-help skills. In turn these adaptations make getting dressed, putting shoes on or going to the toilet much less frustrating and encourage a greater level of independence.

### 5.3.3 Puberty

Typically in boys with Lowe syndrome, while puberty is delayed slightly, it does follow a normal progression.

### 5.3.4 Behaviour

Especially during school age. some boys with Lowe syndrome can develop behavioural problems, in some cases severe, which can interfere with learning, social and family interaction and communication. Dealing with these behavioural problems can require a significant amount of time and work input by parents, school teachers and support staff. In Lowe syndrome such behavioural issues are thought to be a result of the metabolic imbalance caused by the genetic mutation, which affects brain function and development. As such, it may help parents and teachers to view behavioural problems as another medical symptom of Lowe syndrome.

To help improve the learning capacity of Lowe syndrome boys, behavioural psychologists can work with parents and teachers to help them develop effective strategies and methods to manage individual problems. Medications and therapies can be used to help treat these behavioural problems, and so doctors can also be involved in developing treatment and educational strategies.

Boys with Lowe syndrome almost always exhibit behaviour on the autistic spectrum. Autism is a communication disorder that affects how people relate to the world around them. Children and adults with autism have difficulty with social interaction; they may find it difficult to make friends or understand what constitutes appropriate behaviour, often leading to serious behavioural problems. Autism is characterised by three main areas of difficulty, known as the triad of impairments:

- **Social interaction** – people with autism may appear indifferent to other people and unable to relate to them.
- **Social communication** – they may have difficulty using verbal communication. They may also have difficulty with non-verbal communication such as reading facial expressions and body language.
- **Imagination** – they may have difficulty developing appropriate interpersonal play skills.

Autism is viewed as a spectrum disorder. It can range from relatively 'high functioning' people who have some difficulty engaging with others or coping with daily interactions, to those who may have serious behavioural and communication difficulties and may be aggressive towards themselves and/or other people. People

with autism may appear to live in a world of their own and this can be incredibly stressful for families. They may have repetitive and limited patterns of behaviour and a strong resistance to changes in familiar surroundings and routines.

## **Behaviour Categories**

### ***Self-abusive / self-injurious / self-harm***

Boys affected by Lowe syndrome can show self-injurious behaviour, which is defined as intentional, self-inflicted injuring of body tissue that causes damage or leaves marks for more than a few minutes, often done in order to cope with situations the individual finds distressing or overwhelming. Such behaviours can include scratching, banging or hitting body parts or hair-pulling.

In Lowe syndrome, self-injurious behavioural problems generally arise out of frustration or anger, or an inability to properly communicate their feelings or needs. Self-abusive behaviours can often be reduced, either by anticipating the needs of the child or specific triggers that result in self-injury, or by redirecting the behaviour into an activity that does not cause self-injury.

### ***Anxiety disorder***

Anxiety disorder is a term that covers several symptoms associated with excessive fear, uneasiness, apprehension or worry, which can affect both physical and psychological health. These include phobias and irrational fear of objects, situations and future uncertainties, either real or imagined, as well as general anxiety that is not linked to specific incidents or experiences. These fears and anxieties can sometimes become overwhelming and result in 'panic attacks', which manifest as excessive anxiety with dizziness and a rapid pulse.

Anxiety disorder also covers obsessive-compulsive behaviours, where an individual gets locked into a repeated pattern of behaviours (compulsions) or thoughts (obsessions), such as arranging things in a specific order, repeated checking, counting, inflexible routines, excessive washing or obsession with particular objects. Obsessive-compulsive traits can often be time consuming and alienating.

### ***Sexual behaviour problems***

Sexual behavioural problems are when individuals show sexual behaviour that is developmentally inappropriate or aggressive, including both behaviour towards others and self-focused sexual behaviour, eg masturbation. While this behaviour presents as 'sexual' the underlying motivation for it may not be to do with sexual gratification of the individual.

Some types of sexual behaviour are typical at specific developmental stages, and as such parents should try to not overreact in situations when sexual behaviour problems become apparent. However, healthcare and behavioural professionals should be consulted to find out if the specific behaviour should be investigated further. In most cases, explanation of the rules, limiting the time spent in a situation where sexual behaviour occurs, and careful monitoring and praising of appropriate

behaviour is sufficient to encourage children to stop inappropriate sexual behaviour. There are a minority of cases where a sexual behaviour is not typical of normal healthy development and it will be necessary to refer the situation to a mental health professional.

### ***Self-stimulation / repetitive motor behaviour***

Self-stimulation, often referred to as “stimming”, involves repetitive and recurring movements or behaviours such as repeating sounds, words or phrases over and over again, rocking, hand or finger flapping, excessive teeth grinding and complex whole body movements, which sometimes appear to occur at random, but often are stimulated when the child is excited.

The reasons for stimming are not fully understood, but could be because the sensation makes individuals feel good, or feel secure by blocking out unwanted sounds or sights in an overwhelming sensory environment, or to alleviate internal anxiety.

### ***Physical and verbal aggression***

Some Lowe syndrome boys can suffer from physical and/or verbal aggression, where they act out their negative emotions or feelings in destructive behaviour. This can include being verbally aggressive or causing physical harm to another person.

### ***Disruptive behaviour***

It is normal at different ages for children to be naughty, defiant and break the rules from time to time, especially in infancy and adolescence. However, disruptive behaviour disorder describes repeated disruptive behaviour patterns which are outside the norm for a child's age. There are three main clinical disruptive behaviour disorder diagnoses, which are described below:

- Attention deficient hyperactivity disorder (ADHD)
- Oppositional defiant disorder (ODD)
- Conduct disorder (CD)

#### *- Attention deficient hyperactivity disorder*

ADHD, also known as hyperactive/inattentive behaviour, is where individuals display inattention, impulsivity and overactivity. Inattention results in difficulty concentrating and forgetting instructions. Impulsivity means that children may talk over others, are distractible, accident prone and have a short fuse. Overactivity refers to restlessness, fidgeting and difficulty taking turns or staying quiet.

#### *- Oppositional defiant disorder*

ODD describes behaviour that is typically defiant, often in the home and at school, but sometimes also in other situations, and occurs in children and adolescents at any age. Characteristic behaviours in ODD include: defiance of authority figures (teachers, parents) and refusal to obey rules, argumentative, easily angered/irritated,

deliberately aggravating others, resentment and revenge towards others, frequent temper tantrums and seeking to blame others for their own mistakes/bad behaviour.

#### *- Conduct disorder*

Children with conduct disorder show a range of anti-social behaviours that break social norms and rules. These behaviours include the intentional destruction of property, which is seen in some cases of Lowe syndrome. More serious behaviours include acting on destructive urges, threatening and aggressive behaviour, bullying, harming animals or people, stealing and habitual lying.

#### **Social development**

There are a set of unspoken rules that govern how individuals interact with one another at a social level. Most individuals will learn these rules as part of their normal social development, and will be able to function well in social settings without being specifically taught how to. Individuals with Lowe syndrome often engage in social avoidance, where they tend to ignore social cues as they haven't learnt how to read social situations or interact with the people around them. This can cause them to be socially 'awkward' and they often avoid making eye contact with the person they are talking with by focussing on other objects.

#### **Tactile sensory defensiveness**

The process of taking in and interpreting information from our surroundings is called 'sensory processing', and individuals with tactile defensiveness struggle with processing some of this sensory information. Sensory defensiveness is defined as "a tendency to react negatively or with alarm to sensory input which are generally considered harmless or non-irritating by most people".

This can affect all of the senses, and common symptoms include severe dislike of loud, high-pitched or chewing noises, dislike of being touched, intolerance of certain fabrics touching the skin, dislike of foods due to taste, texture or temperature, difficulty maintaining eye-contact and feeling overwhelmed when exposed to a range of sensory stimuli all at once.

#### **Need for sameness**

Need for sameness, also known as 'resistance to change', refers to a condition where individuals have a strong insistence on order and routine in their lives, and can become upset when their routines or surroundings are disrupted, or during transitions between different activities.

This often appears as highly repetitive behaviour patterns, where an individual does or thinks the same thing over and over again, and may include specific rituals that must be done in exactly the same way each time.

#### **Hyper vigilant to correctness**

Hyper vigilant individuals tend to require perfection not only from themselves but also from those around them. When they fail to achieve perfection, hyper vigilant

individuals may become frustrated and withdraw from activities because of the fear of failing. There may also be a need for constant reassurance when doing activities that what they are doing is correct.

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A variety of approaches, including medication, are available for behavioural disorders, some of which focus on treating the behaviour itself, whereas others are aimed at the underlying causes. Some therapies to reduce inappropriate behaviours involve distraction techniques to keep an individual occupied with other activities, or replace the behaviour with safer, appropriate behaviours (avoidance or redirection techniques). Encouraging appropriate behaviour (sometimes known as 'positive reinforcement', see below) is an effective method to reduce behavioural problems, and can easily be used by both parents and carers of boys with Lowe syndrome.

## **Behaviour Management**

Because the behavioural challenges and personalities of each boy with Lowe syndrome vary, so also the techniques for behaviour management will vary from case to case. Often parents are the people best-placed to judge which behaviour management techniques will be effective for their child.

Behaviour management involves two basic principles:

1) *Positive reinforcement*

Appropriate behaviour is modelled to an individual and encouraged by giving them praise or rewards when they demonstrate the desired behaviours.

2) *Negative reinforcement*

Inappropriate behaviour is followed by an undesirable consequence.

In general, positive reinforcement is used to teach and encourage appropriate behaviour in young boys with Lowe syndrome, however negative reinforcement is used in adolescents and adults to reduce or change inappropriate behaviour.

### *Young children (0-5)*

Providing consistent structure and routine is important to young children with Lowe syndrome – children should be informed in advance about any change in the normal routine. Some children with 'need for sameness' (see above), will still struggle with changes to the normal routine, even if told in advance – however, this will improve with time and consistency of change.

As well as structure, children respond well to clear boundaries for behaviour. When taking part in an activity or particular situation, the expectations of how they should behave should be clearly explained beforehand, including a reward system for good/positive behaviour. Focus on positive behaviours can also be encouraged by redirecting children to activities that are constructive and by engaging directly with them during an activity (see also [Positive Reinforcement Techniques](#) below). You may find that setting time limits on activities, even ones they really enjoy, will help reinforce good behaviour, especially when they are rewarded for sticking to time.

### *Older children (6-9)*

As for young children, behaviour management can be used to encourage and reinforce positive behaviour in older children (6-12 years). As tasks become more complicated with age, older children will require clear and consistent instructions on how to complete tasks during the day. Complicated or long tasks should be broken down into shorter, more achievable steps, and visualising this as a chart is a great way to encourage a child to maintain appropriate behaviour. Again, a reward system is a great way to reinforce good behaviour and help children complete activities, and as children grow older what they are rewarded for should change according to what is expected of them, while always remaining consistent and clear.

Similarly, when a child shows inappropriate behaviour, there should be clear and consistent consequences that negatively reinforce such behaviour, and teach them that it is not acceptable. It is important to note that from a young age most children dislike being disciplined in front of other people, so whatever plan you have for misbehaviour should try to prevent this.

Inappropriate behaviours can be controlled or even prevented well before they become major issues. The most important role models for how to behave that a child has in their lives are their parents, and this is particularly true for children with disabilities. It is also important that parents keep in regular communication about behaviour patterns with the child's teachers and doctors to highlight any behavioural changes and discuss what to do about them.

### *Teenagers*

As children grow into teenagers it is essential not only to keep using behaviour management techniques, but also to keep adapting them to meet their needs. It is important to increasingly involve your child in the process as they mature: helping to set expectations and rules, and to decide what the rewards and consequences are. This responsibility will not only help improve their self-esteem but also reinforce the message that positive and appropriate behaviour brings positive benefits, and that they are able to manage and control their own behaviour.

As they go through puberty, with its hormonal and physical changes, and sexual development, teenagers tend to be sensitive about how they look, especially around other people. So being understanding and compassionate is particularly important at these times as well as being a good role model. It is also necessary to have open communication about the physical and sexual changes they are undergoing, and doctors and teachers also play significant roles at this development stage.

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At all ages, the most important thing for a parent is to be a consistent, predictable, patient and fair role model to your child.

It is normal and perfectly natural to have questions and to need support when doing behaviour management. It is vital for parents as they learn to manage a child's behaviour that they know they aren't alone and that professional help and support is always available, especially when difficult or overwhelming situations arise.

## ***Behaviour improvement programs***

Behaviour Improvement Programs combine a number of behavioural techniques, for example positive reinforcement, negative reinforcement and behaviour modification methods, in order to improve a particular behaviour. In this section we look at some of the various assessments that are used both to determine the root causes that underlie a particular behaviour and to establish possible treatment options.

*Environmental Assessment* comprises an investigation into the physical surroundings of the child at particular times, for example their home or school. Such assessments aim to identify specific elements in particular surroundings that may be interfering with a child's day-to-day behaviour or ability to function. So for example, high classroom noise levels may help give rise to misbehaviour or inability to engage in activities – so, adjusting the classroom environment to reduce noise levels will lead to improved behaviour and participation.

*Functional Behavioural Assessment* is a method of evaluating behaviour patterns or specific misbehaviours which are resulting in problems in the home or in the classroom. The Functional Behavioural Assessment is commonly done alongside another assessment called the *Individual Education Plan* (or IEP), which is developed to help each individual child get the best out of their education. The IEP sets out educational targets for each child and a plan of how to achieve them, taking their behaviour into consideration. By determining the motivation and reason for particular behaviour patterns, the IEP informs teachers and classroom support workers how best to help an individual achieve progress.

## **Positive reinforcement techniques**

There are a variety of positive reinforcement techniques, some of which work well for some individuals and not others, and so it is worth trying them out to see what works best for you and your child. This is by no means a comprehensive list, but hopefully will inspire you with different ideas of how to positively reinforce good behaviour in your child.

### ***Using redirection***

Redirection covers a variety of verbal, non-verbal and physical methods to provide a positive transition from an inappropriate behaviour to a desired behaviour by diverting your child's attention. Verbal redirection includes asking your child to do something else. Non-verbal redirection could include using a toy or other activity to distract your child from an inappropriate behaviour. Physical redirection may involve physically moving or guiding your child to another activity.

Here are a few suggestions for how to positively redirect your child:

- redirect the behaviour towards something he loves
- use distraction or a change of scenery

- acknowledge his feelings
- help him find the right words to express himself
- try singing songs, laughing or using positive encouragement to help him enjoy situations he may otherwise find stressful
- let him know that he does have choices he can make
- try to regularly introduce new things so as not to establish too strong a routine
- offer rewards to help motivate him overcome routines
- use visual charts of his schedule for the day.

### ***Using natural and logical consequences***

A natural consequence is something that naturally follows as the result of an action. So for example, if you do not eat the natural consequence is that you get hungry. If you break the law, you will be in trouble with the police. If you are rude to someone they get upset. These consequences happen due to nature, culture and interactions with other people, without direct interference from parents.

Logical consequences are options that are presented by the person in charge that logically follow on as a result of an action - ie the consequence fits the behaviour - which make it easy for a child to understand. Both positive and negative logical consequences can be given. So for example, if a child is told to tidy their room, they can be given the positive logical consequences that if they do tidy it then they can go and play, or the negative one that if they do not then they will also have to tidy the dining room, or both positive and negative consequences together.

- remind him of the negative consequences of his actions and how they affect him
- give him options, explaining what will happen for each choice
- always make the logical consequences reasonable and achievable
- always follow through on both positive and negative logical consequences to make sure that positive rewards are given, and that negative consequences are instituted. Empty promises or demands will lead to confusion and problems.

### ***Using rewards***

Rewards are a great way to encourage your child and reinforce positive behaviours. They should not be given as bribes to make your child behave, but instead should be given to reward your child when they achieve a goal, do something well or make good progress.

### ***Routine / Visual charts / Schedules***

Routines and schedules are a great way to let your child know what they should be doing at what time, and what is coming up next. Visualising this as an easy-to-follow chart will help your child complete activities and transition between them, and will remove some of the burden of responsibility from you, as it is the list that enforces the rules, not you. Schedules work especially well for children with obsessive compulsions who need to always know when and what is happening next, as they can look at the chart instead of asking you. It is important to stick closely to your routine or schedule, and if there are any changes prepare your child for these beforehand.

Designing your chart is an opportunity to involve your child in the process and give them some ownership and responsibility, as well as having fun. Put the chart up in a position where it is easily visible so that your child can see it. For young children it is good to have pictures on the chart to help them understand it.

### ***Using verbal and non-verbal cues to manage behaviour***

#### ***Praise and positive words***

Verbal and non-verbal cues are words or gestures used to remind your child what type of behaviour you expect from them. Praise and positive words have been included in this section because praise can be a very strong verbal reinforcement tool when encouraging the behaviour you want to see. All words of encouragement need to be descriptive, so that your child understands exactly which behaviour you are giving them praise for and that you are encouraging that behaviour to happen again. Verbal reinforcements, like rewards, are most effective when given immediately. CATCH YOUR CHILD BEING GOOD and give extra praise for those behaviours you want to increase.

### ***Using replacement of bad behaviour with an appropriate behaviour***

#### ***Exposure to activities they resist***

When using this technique, think about the appropriate activities your child enjoys and when an inappropriate behaviour occurs replace what they are doing with the new activity. A sensory box is a replacement tool that can be used to replace the offending behaviour. A sensory box can be filled with rice, sand or water and toys that your child can manipulate are placed inside the box. Be sure to place items in the box that are safe for your child to handle. Many children with Lowe syndrome are resistant to feeling different textures. A sensory box can also be used to slowly expose children to new textures.

### ***Ignoring behaviour/ Letting behaviour happen***

To use this technique effectively you must ignore the behaviour completely and consistently. That means no eye contact, no physical contact and no verbal contact with your child when the behaviour occurs. Make sure your child is in a safe place when using this technique and if necessary walk away from your child if you are unable to ignore the behaviour. In some children the behaviour will get worse before it gets better, but by being consistent and ignoring the behaviour every time it

happens the negative behaviour will decrease. This type of behaviour modification can be used with praise, so as you ignore the inappropriate behaviour, praise the behaviour you want to increase. This allows your child to get attention for appropriate behaviour and lets a child know what behaviour you expect.

### ***Anticipating behaviour / Triggers***

Triggers are situations or behaviours that cause distress in your child. When anticipating the behaviour or trigger it is important to know what causes your child to act up or lose control. Be ready to remove your child from these types of situations. By verbally acknowledging your child's feelings in these situations you can help your child become aware of their own triggers.

Start developing strategies with your child to reduce frustrations, covering their ears when a noise is too loud, preparing for school the night before by making lunch or laying out clothes to avoid morning melt downs. Be prepared to offer alternative activities to either soothe them, such as rocking, a warm bath, quiet music or a more active activity, bouncing on a ball, going to the playground, pushing against the wall or other physical activities to redirect anger or frustration.

## **5.3.5 Education**

The right education for boys with Lowe syndrome depends upon several factors, including the boy's individual needs and community resources.

Children with Lowe syndrome will have Special Educational Needs (SEN), such as general learning difficulties and/or Autistic Spectrum Disorder (ASD), and require specialist education. Sadly, there is currently very little specialist education available: across the UK there are about 7,500 places for the (minimum of) 90,000 children with autism. It has been shown that early intervention is the most effective way to enable children to learn appropriate behaviour and it is important for children to be assessed as early as possible to facilitate them getting appropriate education.

Children with Lowe syndrome will need a statement of SEN. This is a legal document that lays out the details of special needs which the child has. The statement then goes on to outline the specific help that will be made available to meet the child's special needs. This is called special educational provision.

For information on special educational provision in your area, contact your Local Education Authority.

## **5.3.6 What does 'special educational needs' mean?**

The term 'special educational needs' (SEN) has a legal definition, referring to children who have learning difficulties or disabilities that make it harder for them to learn or access education than most children of the same age.

Many children will have SEN of some kind at some time during their education. Help will usually be provided in their ordinary, mainstream early education setting or school, sometimes with the help of outside specialists.

If your child has SEN, they may need extra help in a range of areas, for example:

- schoolwork
- reading, writing, number work or understanding information
- expressing themselves or understanding what others are saying
- making friends or relating to adults
- behaving properly in school
- organising themselves
- sensory or physical needs which may affect them in school.

### ***Your child's progress at school***

Children make progress at different rates and have different ways in which they learn best. When planning lessons based around the National Curriculum, your child's teacher will take account of this by looking carefully at how they organise their lessons, classroom, books and materials. The teacher will then choose suitable ways to help your child learn from a range of activities (often described as 'differentiating the curriculum').

If your child is making slower progress or having particular difficulties in one area, they may be given extra help or different lessons to help them succeed. Just because your child is making slower progress than you expected or the teachers are providing different support, help or activities in class, this does not necessarily mean that your child has SEN.

### ***Getting help for your child***

Your child's early years are a very important time for their physical, emotional, intellectual and social development. When the health visitor or doctor makes a routine check, they might suggest that there could be a problem. If you have any worries of your own, you should ask for advice straightaway.

You should first go to your child's class teacher, the SENCO (the person in the school or preschool who is responsible for coordinating help for children with special educational needs) or the head teacher.

You could ask them if:

- the school thinks your child is having difficulties and/or has SEN
- your child is able to work at the same level as children of the same age
- your child is already getting extra help
- you can help your child.

If your child's school agrees that he or she has SEN in some areas, they will adopt a step-by-step approach to meeting these needs:

- Special educational needs: a step-by-step approach
- Identifying special educational needs in under fives
- Getting help for special educational needs in under fives.

### ***Special educational needs: Basic principles***

There are a number of basic principles that all those involved in your child's education will consider. When talking to your child's teachers, there are some basic points to bear in mind:

- if your child has SEN their needs should be met and they should receive a broad, well-balanced and relevant education
- your views should always be taken into account and the wishes of your child should be listened to
- your child's needs will usually be met in a mainstream school, sometimes with the help of outside specialists
- you should be consulted on all the decisions that affect your child
- you have a vital role to play in your child's education.

If your child has SEN, there are also a number of organisations that will be of help.

To find out more visit

[www.direct.gov.uk/en/Parents/Schoolslearninganddevelopment/SpecialEducationalNeeds/DG\\_10016184](http://www.direct.gov.uk/en/Parents/Schoolslearninganddevelopment/SpecialEducationalNeeds/DG_10016184)

## **5.3 Adulthood**

Throughout life, most boys with Lowe syndrome live at home with their families. Some families decide that placement in a residential setting is appropriate due to the complexities of medical management, educational needs, or severe behaviour problems. As adults, some individuals have successfully made the move into a group home while a few live independently. Some work in sheltered workshops or participate in other special programs for adults with disabilities. Parents should consider establishing legal guardianship of their son when he turns 18 years old.

## **'Toolkit of Professionals'**

If you have a child with Lowe Syndrome you are likely to encounter a number of professionals including:

Endocrinologist (metabolism specialist)

Ophthalmologist (eye specialist)

Physiotherapist

Occupational Therapist

Speech and Language Therapist

Kidney specialist

Educational Psychologist (to assess Special Educational Needs)

GP

# 6. Genetics and the molecular basis of Lowe syndrome

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### Summary:

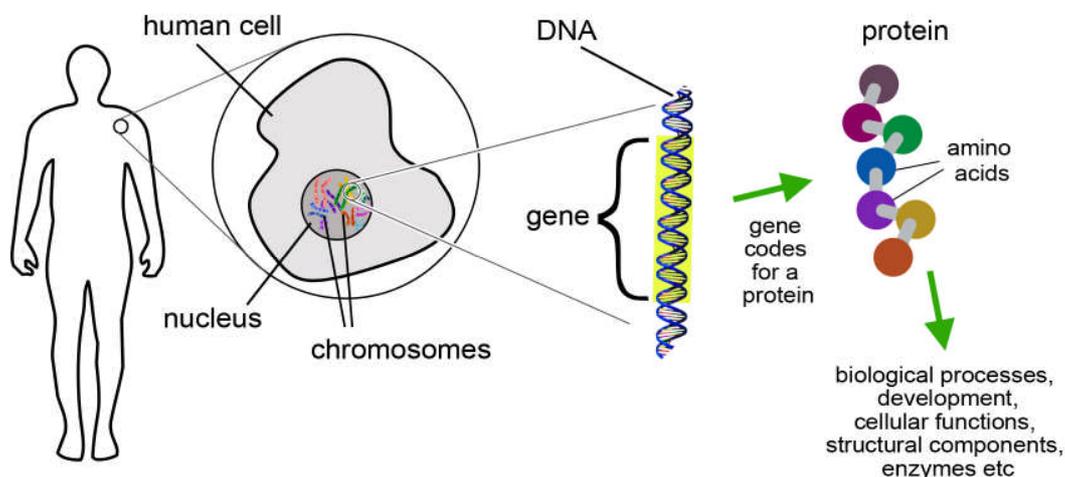
- Lowe syndrome is caused by a genetic mutation
- It can be inherited or may arise spontaneously
- The affected gene (*OCRL*) codes for a protein called phosphatidylinositol 4,5-biphosphatase which is involved in many functions in the body
- Lowe syndrome almost exclusively affects males as the mutated gene is on the X chromosome (males have only one (XY), whereas females have two (XX)).

## 6.1 Introduction to genetics

Low syndrome is a genetic disease, which means that the condition is caused by a defective gene. We inherit our genes from our parents – half from our mother and half from our father. Genes are the 'blueprint' for the body – each gene is made up of DNA and gives the information needed to make a component of the body. If there is an error in this information then the component will not be made properly and this may cause disease or disability. It is a bit like trying to use a set of instructions to build a car. A small mistake in the instructions, a missing piece and a major part doesn't work although the rest of the car looks fine.

The body is made up of building blocks called 'cells'. In a newly fertilised egg, all of the cells are the same and they are known as 'embryonic stem cells' as they have the potential to become any kind of cell. As the egg develops into an embryo, the cells 'differentiate' and take on particular roles in the body, eg they become skin cells, kidney cells, muscle cells, brain cells, etc. Once a cell has differentiated and taken on a function, it cannot change into another kind of cell.

Almost every type of cell in the body contains a copy of the 'blueprint', the genome, made up of thousands of genes. To carry out their function in the body, each cell makes special molecules called proteins, which do all the work in the body, metabolising food to make energy, breaking down toxins, enabling growth, regulating bodily functions, etc. The genes are the set of instructions used to make proteins. If there is a mistake in the set of instructions then a protein may not be made properly and this may lead to disease.



Chromosomes are structures made up of DNA which include many genes joined together. Every cell in the human body (except red blood cells, egg cells and sperm) contains 46 chromosomes, made up of 23 pairs. One of each chromosome pair is inherited from the father and the other from the mother. In reproductive cells, ie eggs and sperm, there is only one of each of the 23 chromosomes, so that at conception, when sperm and egg fuse, it creates a fertilised embryo cell complete with 46 (23 pairs) of chromosomes, from which a new human being will develop.

Of the 23 pairs of chromosomes, 22 contain genes that are involved with development and maintenance of most characteristics of the body, from determining eye colour and height, to producing enzymes to digest food. However, the twenty-third pair is very different as it is involved in determining the gender of the offspring – females have two ‘X’ chromosomes (XX), and males have one ‘X’ and one ‘Y’ (XY).

As females are XX, each of the eggs will carry one or the other of the mother’s X chromosomes (but not both). Similarly, male sperm will contain either the X or the Y chromosome from the father (but not both together). Therefore, sperm with an X chromosome will give a girl (XX), and sperm containing a Y will a boy (XY).

## 6.2 Questions about genetics

### 6.2.1 How do genes cause disease?

Genes are described as the building blocks of life, and are made of DNA (deoxyribonucleic acid), which is packaged into chromosomes. DNA is made up of lots of small units (bases) that form a long thread. There are 4 kinds of base known as A, T, C and G, and these 4 letters are the basis of the code that the genes are written in. Their order and number varies depending on the instruction: just like building up words from the alphabet where the letters in the words need to be in the correct order to make up a sensible instruction, similarly in a gene the bases A, T, C and G need to be in the correct sequence to build up the correct gene product (protein). Hundreds or even thousands of these letters may make up the instruction for one protein. A mistake in just one of these letters can mean that the protein is not made properly – just as a small typo can make a word unrecognisable or converted into a different word altogether and render the sentence incomprehensible.

Through the proteins that they give the code for, genes ultimately control all of the functions in every one of the billions of cells in the human body. The complete range of chemical, physical and physiological processes that occur in our bodies is known as our metabolism. When a mutation arises in a gene, it may change the function of the protein it codes for and consequently affect one or multiple parts of the metabolism, leading to an imbalance that causes a disease. This is known as an ‘inborn error of metabolism’, and is what happens in Lowe syndrome.

### 6.2.2 Mutations: How do genetic mistakes happen?

A defective gene is caused by a ‘mutation’ – a change in the DNA sequence of the gene. Most mutations of genes occur spontaneously, usually for unknown reasons. They may involve just a tiny part of the DNA in a gene. They are not caused by being exposed to medicines or alcohol or emotional events during pregnancy. Mutations in DNA can be caused by chemical or radiation damage, but can also just arise spontaneously without a specific discernable cause, usually not caused by any fault or

action of the individual. Depending upon exactly when and in what cell a genetic mutation occurs, it may become permanently integrated into an individual's DNA, and potentially passed on to the next generation. In this way, genetic disorders can become inherited in families.

There is no single common mutation in the *OCRL1* gene involved in Lowe syndrome. Different families usually have different mutations.

Lowe Syndrome occurs when there is a mistake in the *OCRL1* gene that is the template to make the enzyme (a kind of protein) called phosphatidylinositol 4,5-bisphosphate 5 phosphatase. This enzyme is involved in many metabolic pathways in the body and without it several areas of the body are unable to function properly, causing disability. These include the eyes, brain, central nervous system, bones and kidneys. These effects are described in [Section 4: Medical Features](#).

### 6.2.3 How is Lowe syndrome inherited?

There are a number of ways in which a boy might be born with Lowe syndrome:

#### 1) Inheritance from 'carrier' mother

Females who have a defective copy of the *OCRL1* gene are called 'carriers', because they carry the genetic mutation and can pass it on to their children. Even though they have a defective version of the *OCRL1* gene, they do not show Lowe syndrome symptoms because they also have one normal copy of the gene to compensate. A carrier may have inherited the faulty gene from her mother, or it may have been a spontaneous mutation, in which case she will not know that she is a carrier for the disease.

Once a child with Lowe syndrome is born into a family, the mother should be tested to see if she is a carrier, as this may affect future pregnancies. Her female relatives can also be tested for carrier status to determine if they are at risk of having a child with Lowe syndrome (see [Section 6.3.1 Carrier detection](#) and [Section 6.3.2 Non and atypical carriers](#)).

#### 2) New mutations

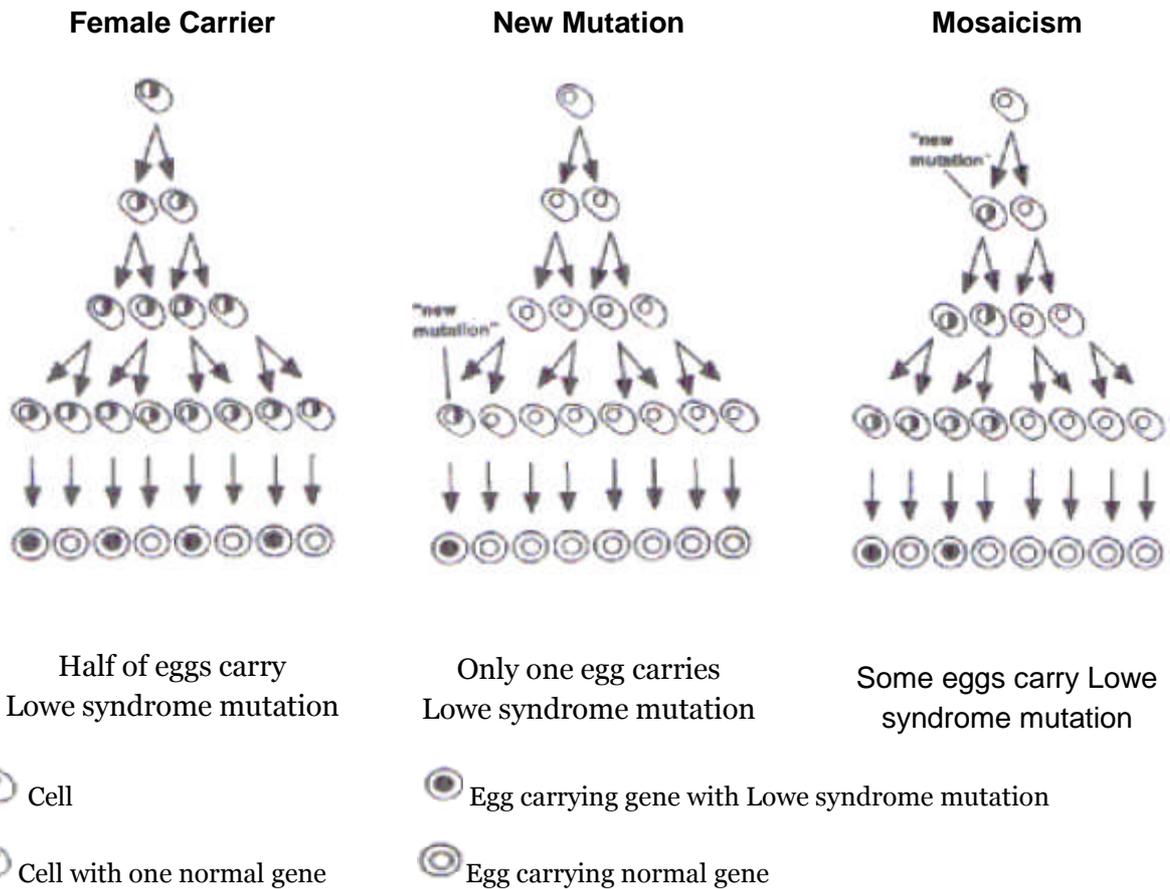
Some boys are the first and only individuals affected by Lowe syndrome in their families, and their mothers do not carry a faulty copy of the *OCRL1* gene. In these cases the genetic mutation occurred in the single egg that was fertilised and developed into the boy with Lowe syndrome, often referred to as a "new mutation". Just as for any such disease, this is a random event that cannot be predicted and is not the result of any 'fault' on the part of the mother.

In this case the boy is the first person with this faulty gene, so the mother is not a carrier and her risk of having another boy with Lowe syndrome or a female carrier is the same as that for non-carrier females in the general population – very low. To

determine if Lowe syndrome is due to a new mutation, the mother of a boy with the first case of Lowe syndrome in a family should undergo carrier testing.

### 3) Genetic mosaicism

As well as families where Lowe syndrome is passed on by carrier mothers and families where Lowe syndrome arises as a new mutation, in some rare cases the mother may have had a new *OCRL1* mutation occur at some point in her development. In such cases this new mutation will only be present in some of the cells in her body that were formed from the original cell with the mutation, which may include cells in her ovaries that go on to produce egg cells. When some cells in the body carry a mutation, and others don't, is known as mosaicism, as shown in the figure below. The other cells in her body may not carry the genetic mutation and therefore she may not show any of the signs of being a carrier, for example the eye examination. However, in this case more than one egg cell will carry the mutated gene, so there is an increased risk of having another boy with Lowe syndrome or a daughter who is a genetic carrier.



### 6.2.4 Why do only boys get Lowe syndrome?

The *OCRL1* gene is found on the X chromosome. As one X is always inherited from the mother and either an X or a Y is inherited from the father, each with a 50:50 chance, for each pregnancy there is a 50:50 chance of having a boy or a girl.

Some diseases are known as 'X-linked' diseases, which means that the gene involved is located on the X chromosome - they typically only affect males who only have one, faulty copy of the mutated gene. Females are often unaffected or only mildly affected by the disease because, even though they may have a faulty copy of the gene on one X chromosome, they also have a normal, functional copy of the gene on the other X chromosome.

Since the early 1960's, physicians have known that the defective gene that causes Lowe syndrome – *OCRL1* - is located on the X-chromosome. All males who have an X chromosome containing a defective copy of *OCRL1* (X\*Y) will show symptoms of Lowe syndrome, since the Y chromosome does not contain an equivalent copy of the *OCRL1* gene to compensate for the faulty gene. Females who carry one faulty copy of the *OCRL1* gene (XX\*) do not develop the full symptoms of Lowe syndrome because they also have a normal copy of the gene (however some carrier females develop cataracts in early/mid-adulthood).

### 6.2.5 What's the probability of having a child with Lowe syndrome?

Women who are carriers of Lowe syndrome have one X-chromosome with the normal gene and one X-chromosome with the Lowe gene.

- For a male child, there is a 50% chance of having Lowe syndrome. If he inherits the X chromosome containing the normal copy of the gene from his mother, he'll be unaffected (normal). But there is an equal chance of inheriting the X chromosome with the faulty *OCRL1* gene, and because he inherited a Y chromosome from his father, he will have Lowe syndrome.
- For a female child, there is a 50% chance she will also be a carrier for Lowe syndrome. There is a 1 in 2 chance she will inherit the normal X chromosome from her mother to accompany the normal X she inherits from her father, and an equal chance she will inherit the defective X chromosome and be a carrier like her mother.

So, for any given pregnancy a female carrier has a 1 in 4 chance (25%) of having a boy affected by Lowe syndrome, a 1 in 4 chance of having a girl who is also a carrier and 1 in 4 chances of having an unaffected boy or an unaffected girl. This is also displayed below in the diagram of X-linked inheritance of Lowe syndrome.

These probabilities apply to women who are genetic carriers of Lowe syndrome. However, as discussed above, sometimes mutations in *OCRL1* can occur spontaneously, and the affected boy is the first individual in the family with Lowe

syndrome. Determining whether or not the mother of a Lowe syndrome child is a genetic carrier, is very important in predicting the outcome of future pregnancies and possibly also the pregnancies of her female relatives.

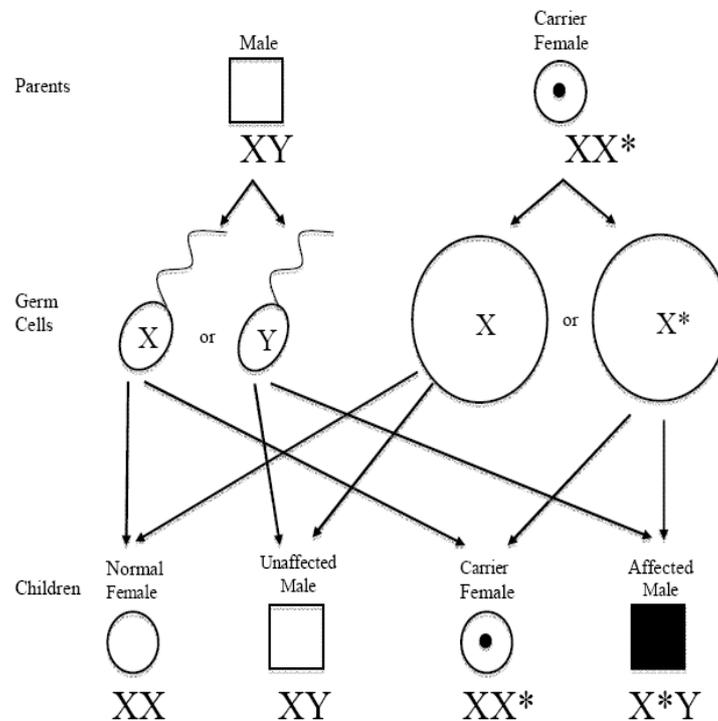


Diagram of X-linked Inheritance

#### 4.2.6 What clinical tests are available?

Lowe syndrome is caused by a deficiency in the enzyme phosphatidylinositol 4,5-biphosphate 5 phosphatase as a result of a genetic mutation. There are a number of clinical tests that can be used to confirm the diagnosis of Lowe syndrome in boys:

##### 1) Biochemical testing

The enzyme deficiency can be directly detected using a simple and reliable biochemical test that assays enzyme function. This enzyme test is commonly used in the diagnosis of affected boys, which requires a small skin biopsy, as well as for prenatal diagnosis, which requires either chorionic villus sampling or amniocentesis. Blood samples cannot be used for the enzyme test.

##### 2) Genetic testing

Lowe syndrome can also be diagnosed by directly analysing the whole sequence of the *OCRL1* gene to look for mutations responsible for the disease. The gene can be sequenced from a standard blood sample. To date, worldwide well over 100 separate mutations have been found in the *OCRL1* gene in different Lowe syndrome patients, and many affected families have a unique *OCRL1* mutation.

## 6.3 Gene therapy

Gene therapy is used to supplement a defective gene with a working version. In particular there is a lot of research into using it to treat hereditary diseases. The idea is that a 'normal' gene is introduced into cells to replace an 'abnormal' gene. The biology involved in human gene therapy is enormously complicated and it is in the very early stages. A major difficulty in gene therapy is delivering the working gene into the cells without disrupting any other genes or the working of the cell. Before gene therapy can be used effectively, techniques need to be developed and diseases need to be better understood.

Lowe syndrome affects a variety of different tissues in the body and the mechanisms by which these tissues are disrupted by the mutated gene are not fully understood. For this reason, it may be very difficult or even impossible for Lowe syndrome to be treated with gene therapy – at least in the foreseeable future.

## 6.4 Genetic counselling

If there is a case of Lowe syndrome in a family, the female relatives of the mother may also be at risk of having a child with Lowe syndrome. As described above, Lowe syndrome may either be inherited from the mother or be caused by a spontaneous mutation. In the former case, there is a possibility that other women in the family may also be carriers of the disease and therefore might also be at risk of having a child with Lowe syndrome.

Women who are at risk of being carriers include the mothers and sisters of affected boys, as well as the boy's maternal aunts and their daughters. Determining whether the mother of a child with Lowe syndrome is a carrier is important for both her future pregnancies and those of her female relatives.

If she is not a carrier then the mutation that caused the syndrome was spontaneous and other family members are no more likely to be affected.

Couples with a high chance of having a child affected with Lowe syndrome should explore options for family planning with the guidance of a doctor/genetic counsellor, who can help determine the chances of having a child with Lowe syndrome.

### 6.4.1 Carrier detection

The carrier status of some females can be inferred from their family history, eg a mother with a Lowe syndrome boy and a previous case of Lowe syndrome in her family can be presumed to be a genetic carrier. However, even if there is no known family history, the mother of a boy with Lowe syndrome may be a carrier due to her having inherited a mutation, or mosaicism in her ovaries, and so needs to undergo testing to see whether she is a carrier or not.

Unlike for boys who have Lowe syndrome, carriers cannot be diagnosed using simple blood or skin biochemical testing.

However, at-risk females can be tested to see whether they carry Lowe syndrome or not by an eye examination which requires the use of drops to dilate the pupils. In around 95% of Lowe syndrome carriers, especially following puberty, there are small changes in their eye lenses, appearing as tiny opaque dots in a characteristic pattern. Typically these flecks do not affect the vision and, unless specifically looked for, can be missed or dismissed as normal variations. As such, specialists must insist the eye test is done only by ophthalmologists experienced at looking at these subtle variations seen in Lowe syndrome carriers.

If an at-risk female shows signs of characteristic lens opacities then she is a Lowe syndrome carrier, but if opaque flecks aren't visible, she is probably not a carrier. However, this is not an absolute diagnosis, as sometimes lens opacities are not present in carriers, especially in girls before puberty. While these flecks do not usually cause problems in sight, a number of carriers have developed cataracts in their 20s–40s, which require surgical removal.

To confirm whether a female is a carrier, DNA sequence analysis can be used to see if a specific mutation in the *OCRL1* gene is present. In most families, the genetic mutation causing Lowe syndrome is unique, so the gene sequence of an affected male can be analysed to find the specific genetic change that causes the disease. This can then be compared to the *OCRL1* sequences of at-risk females to see if they also carry that mutation.

If the specific genetic mutation that causes Lowe syndrome isn't known, then members of families with a history of Lowe syndrome can be tested by 'linkage analysis', where a series of DNA sequence markers near to the *OCRL1* gene are used to trace the inheritance pattern of the mutant gene. This can be used to show if an individual received the faulty gene by showing which set of DNA markers they inherited.

### 6.4.2 Non- and atypical carriers

If a mother of a boy with Lowe syndrome has a normal eye examination (ie, no characteristic opaque flecks in the lens), there are 3 possible explanations:

- 1) Most commonly, the mother is not a carrier and the disease is due to a new genetic mutation in one of her eggs. Her risk of having another child with Lowe syndrome is no more than for any other non-carrier female in the population – very low.
- 2) More rarely, the mother is a carrier but is in the 5% group who do not show the characteristic opacities in their lenses. If so, for each pregnancy the probability of her having another boy with Lowe syndrome is 1 in 4 (25%). In this case, her female relatives are at risk of being carriers.
- 3) Most rarely, she may have mosaicism for the Lowe syndrome mutation in her ovaries (see [Section 6.2.3](#)). If this is the case, she will have additional eggs

that carry the defective *OCRL1* gene, however the cells in her eyes may not carry the mutation and so show no signs of opacities in the lenses. The risk of her having another boy with Lowe syndrome or a carrier daughter is much greater than in the general population, but not as high as for a full genetic carrier.

Sadly, genetic mosaicism cannot be reliably detected using biochemical or molecular tests. Therefore, due to the potential for mosaicism, even women with normal eye examinations may be offered prenatal testing for Lowe syndrome.

If a mother with an affected child is either a non-carrier (1) or has mosaicism for the mutated *OCRL1* gene (3) then her close female relatives (except for daughters in the case of mosaicism) are not at risk for carrying the mutation - in either case the faulty copy of *OCRL1* occurred as a new genetic mutation within the mother herself.

See the table below for a summary.

**Probability of having a boy with Lowe syndrome or a carrier daughter depending on genetic status of the mother**

<b>Mother</b>	<b>Probability of having a son with Lowe syndrome</b>	<b>Probability of having a Lowe syndrome carrier daughter</b>	<b>Probability that female relatives could be carriers</b>
Non-carrier	General population risk (very low)	General population risk (very low)	General population risk (very low)
Carrier	50%	50%	Increased significantly above population risk but precise risk differs
Mosaic (rare)	Increased significantly above population risk but precise risk differs	Increased significantly above population risk but precise risk differs	General population risk (very low)

**6.4.3 Family planning**

There are a number of family planning options for couples at-risk of having children with Lowe syndrome. Some couples consider prenatal testing or pre-implantation diagnosis, whereas others decide to take their chances with each pregnancy, and still others consider fostering / adoption or egg donation from non-carrier females.

There are many factors that influence the decisions a couple makes about family planning, including for example personal views, cultural, moral and religious beliefs, as well as financial and insurance considerations and the services available in different countries. Fundamentally, whatever a couple decides, they must be comfortable with their family planning choice both at the time and in the future.

### *Prenatal testing:*

Prenatal testing is an established and widely available technique used to find out if a foetus is male or female. In addition, if a foetus is male, Lowe syndrome can be diagnosed prenatally using the same biochemical enzyme analysis used to test individuals postnatally (*see Section 4.1*). This can be done even if the carrier status of the mother is unclear or there is a risk of mosaicism, and is irrespective of whether the specific *OCRL1* mutation involved has been identified.

There are two methods for prenatal testing: chorionic villus sampling (CVS) done at 11-13 weeks, or amniocentesis done at 15-18 weeks. While the sampling procedures can be done regionally in local centres, currently the biochemical enzyme analysis is only available at the Biochemical Genetics Laboratory, Baylor College of Medicine, Houston, Texas. Please contact the *Lowe Syndrome Trust* for further information. Where possible, prenatal testing should be planned in advance of a pregnancy.

### *Pre-implantation diagnosis:*

An experimental technique called pre-implantation genetic diagnosis has been suggested as another option for some couples. This technique involves in vitro fertilisation (IVF) and then testing the DNA in one cell of the fertilised eggs for the presence of a disease-causing genetic alteration. Any embryo that is found to lack the disease-causing alteration (and is therefore normal) could be implanted into the womb. Pre-implantation genetic diagnosis has been used successfully in a few genetic disorders but has not been tested rigorously in Lowe syndrome and therefore remains a theoretical possibility. Pre-implantation genetic diagnosis is a DNA test that would require accurate knowledge of the family's specific gene alteration. The biochemical enzyme diagnosis for Lowe syndrome cannot be used because the amount of material available for study is too small.

## 6.5 Lowe syndrome and Dents disease – 2 ends of a spectrum

*Dent disease:* In 1964, Dr Dent and a colleague in London described two men affected by rickets in childhood associated with urine wasting of phosphate, calcium, amino acids and small proteins. In addition, they had a decreased kidney filtration rate. Interestingly, one of the two men described also had decreased intelligence. With time, more descriptions of patients affected by similar symptoms emerged, many of them developing kidney stones and renal failure. As in Lowe syndrome, the disease affected exclusively males, occurred in families and could be passed on by women, who showed no obvious symptoms.

In 1996, it was shown that mutations in a gene on the X chromosome called *CLCN5* could cause Dent disease. However, it was also noted that in about a third of patients with the clinical diagnosis of Dent disease no mutation in this gene could be found, suggesting that other genes could also cause Dent disease. In 2005, careful studies in one large family showed that all affected men had a mutation in *OCRL*, the gene

associated with Lowe syndrome. Mutations in *OCRL1* were then also found in some other patients with Dent disease. These patients are now often referred to as having Dent2 disease to distinguish them from patients with mutations in *CLCN5* (Dent1 disease).

The surprising finding of *OCRL1* mutations in some patients with Dent disease has prompted the question of how mutations in one gene – *OCRL1* - can cause two apparently distinct diseases: Lowe syndrome in some, Dent disease in others. Clinical observations, however, suggest that the two diseases may be closer to each other than originally thought: several Dent2 patients have reduced or borderline intelligence, and, in fact, this had already been noticed by Dr Dent in one of his original two patients. Nevertheless, other patients with Dent2 disease have normal or even above average intelligence. When looking at large cohorts of patients with Dent1, Dent2 or Lowe syndrome, it was noted that average growth is more compromised in Dent2 patients than those with Dent1, but less than in Lowe syndrome. (Note: individual Dent2 patients can have perfectly normal growth, but the average of all Dent2 patients is less than normal). Both Dent2 and Lowe patients typically show elevated levels of certain muscle proteins in their blood, suggesting that muscle may also be mildly affected in both diseases.

Considering also the variability of severity of symptoms in Lowe syndrome it becomes apparent that there is no clear distinction between Dent2 disease and Lowe syndrome. Whereas Dent1 disease only affects the kidney, the spectrum of symptoms in Dent2 disease can range from apparent exclusive kidney manifestations to involvement of other organs, notably brain and muscle, in overlap with Lowe syndrome. Thus, the distinction between the two diagnoses rests mostly on the presence of eye abnormalities. When considering that this can occasionally be quite mild in Lowe syndrome, the distinction becomes somewhat arbitrary in those patients.

Nevertheless, in most patients with *OCRL1* mutations the clinical diagnosis is clear: those boys with the typical eye, brain and kidney abnormalities are diagnosed with Lowe syndrome, whilst those with (almost) exclusive kidney problems have Dent2 disease. Yet, we do recognise that there is a fluid border between the two diagnoses. Perhaps this can actually help to identify treatments for Lowe syndrome: if we could find out why some patients seem to have only kidney problems with *OCRL1* mutations and not the full spectrum of Lowe disease, this might provide clues for the treatment of symptoms in eye and brain.

# 7. Research into Lowe syndrome

Historically, there has been very little research into Lowe syndrome as it is believed to be very rare, although it is important to note that as yet there is no official clinical database giving numbers worldwide – the *Lowe Syndrome Trust* is seeking to address this. The lack of research projects is starting to change as the we raise funds to drive this forward.

This section gives a quick history of how research into Lowe syndrome has developed since its initial discovery and explains some of the difficulties associated with the research, current research directions and the work of the *Lowe Syndrome Trust*.

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## 7.1 Early research 1952 - 1982

Lowe syndrome was first recognised as a disease in 1952 by Drs. Lowe, Terrey, and MacLachlan at the Massachusetts General Hospital in Boston.

In 1954 the specific form of kidney problem associated with the syndrome was recognized. X-linked inheritance was suggested in 1957, and the ability to identify female carriers by eye examination was confirmed in 1976. Research was held back as the biochemical manifestations of Lowe syndrome were found to be too nonspecific for easy investigation as the syndrome affects such a wide array of pathways. There was no single abnormal metabolite which would point to a specific pathway to investigate. Furthermore, there were no naturally occurring animal models for the disease. Researchers were restricted both by the limitations placed on investigations using human patients, and a lack of human research subjects due to the rarity of the disease.

Significant progress has only begun in the past decade as several factors that have frustrated researchers' efforts over the years have changed. Lack of funding for research projects, lack of awareness, technical barriers to research and a lack of research subjects have all hampered research progress.

## 7.2 Developments 1983 - present

### 7.2.1. Identification of the genetic basis of Lowe syndrome

The dramatic advances in the field of genetics during the past decade have opened new avenues of research and have led to significant advances in understanding Lowe syndrome. In 1995, it was discovered that Lowe syndrome is caused by a particular enzyme deficiency due to a defective gene. This development has indicated clear avenues for research.

The first big step towards identifying the underlying defect took place in 1986 when Drs Lewis and Nussbaum and their colleagues at Baylor College of Medicine succeeded in assigning the Lowe syndrome gene to a small region in the middle portion of the long arm of the X-chromosome. Subsequent work by many collaborating scientists ultimately culminated in identifying the exact identification of the gene in 1992. The gene site for Lowe syndrome is known as *OCRL1*. Three years later, Dr. Nussbaum and his colleagues, then at the National Institute of Health, announced the discovery that the defective gene causes a deficiency of an enzyme that is essential to inositol metabolism. The enzyme phosphatidylinositol 4,5-biphosphate 5 phosphatase is essential to normal metabolic processes that take place in a part of the cell called the Golgi apparatus. Because this enzyme is deficient in Lowe syndrome, cell functions that are regulated by the Golgi are abnormal, leading to developmental defects such as cataracts and kidney and brain problems.

Research shows that the *OCRL1* gene may also be implicated in other rare genetic diseases such as Dent's disease, a discovery that may shed light on the relationship between genetic mutations and clinical diseases.

### 7.2.2 Research into cell signalling

Current research is directed toward understanding how and why the enzyme deficiency causes so many difficulties. The role of phosphatidylinositol metabolism in normal Golgi function and in Lowe syndrome is being investigated extensively by researchers.

The defective OCRL enzyme in Lowe syndrome means that carriers cannot control levels of a molecule named PIP<sub>2</sub>, which in turns leads to development of the symptoms of Lowe syndrome. PIP<sub>2</sub> belongs to an important group of signalling molecules named inositol lipid phosphates, which are involved in pathways that malfunction in a number of other diseases, including some cancers, neurodegenerative disorders and heart disease.

This research is investigating the core underlying biochemistry of the disease and will lead to a better understanding of the disease, facilitating improved diagnostic tests, the development of an animal model and may possibly lead to a cure through the development of a drug that can replace the missing enzyme.

### 7.2.3 Development of diagnostic and carrier tests

The development of diagnostic and carrier tests have also been the subject of recent and ongoing research projects. The discovery of the enzyme deficiency led to the development of a simple and reliable diagnostic and prenatal diagnostic test. A biochemical test - a direct assay of the enzyme phosphatidylinositol 4,5-biphosphate 5 phosphatase - was initially developed in 1996 .The enzyme assay is now commonly used to diagnose affected patients as well as to carry out prenatal diagnosis.

Biochemical testing is not, however, effective for carrier detection. For laboratory carrier testing, the specific change (mutation) in the DNA sequence that causes the disease can be used to identify carriers. To date, over 100 different mutations have been found in patients with Lowe syndrome. Thus, most families typically have a mutation unique to their family. DNA sequencing is the only way to establish which mutation is responsible for a particular case of Lowe syndrome. Once the mutation has been identified, other female relatives can be tested for carrier status if this is needed.

This type of genetic mutational analysis is currently still an expensive procedure not commonly available through routine clinical laboratories. In some families with a strong family history of Lowe syndrome, DNA markers near the mutant gene may be used to trace the inheritance of the abnormal gene in the family without knowing the specific mutation in the gene. This approach, called "linkage," is carried out by specialized genetic diagnosis labs. The eye examination of at-risk females (see

*Section 6: Genetics*) currently remains the standard method for determining carrier status. However, an applied research project currently underway at the National Institutes of Health and funded by the Lowe Syndrome Association is directed towards streamlining and improving the process of searching for mutations. The LSA hopes that this project will lead to the development of a simple and reliable carrier test that will be available in clinical settings within the near future.

#### 7.2.4 Clinical research

Researchers at the National Institutes of Health in the USA have studied clinical (ie medical) aspects of the syndrome in a large number of individuals over a span of several years during the 1980s and early 1990s. Their discoveries led to a better understanding of the natural course of the syndrome and better treatment techniques for many of the problems. Other important research projects include a study that helped to establish a causal link between the syndrome and behavioural problems. Much work remains to be done in the area of clinical research.

Research projects are currently underway to investigate Lowe cataracts and kidney problems.

The UK *Lowe Syndrome Trust* is currently working on establishing a clinical database, which can be used by researchers to aid their work in both molecular and medical fields.

#### 7.2.5 Brain and tissue bank

In the USA, the LSA supports research is by encouraging its parent members to register with the Brain and Tissue Bank (BTB) for Developmental Disorders at the University of Maryland. The BTB collects relevant tissues after surgery or after death and stores them for future research purposes. Supported by the National Institute of Child Health and Human Development, the BTB is dedicated to the "improved understanding, care and treatment of developmental disorders." LSA families are encouraged to consider registering with the program.

The Lowe Trust in the UK is working to establish a similar bank to aid research.

### 7.3 The Lowe Syndrome Trust and research

Good medical research requires a partnership between scientists, physicians and affected families. Cooperation and sharing of ideas has led to rapid advances in understanding the cause of Lowe syndrome and may lead to more effective therapies. By providing funds for medical and scientific research, the *Lowe Syndrome Trust* helps to encourage innovative thinking and interest in a rare condition that otherwise might go unnoticed.

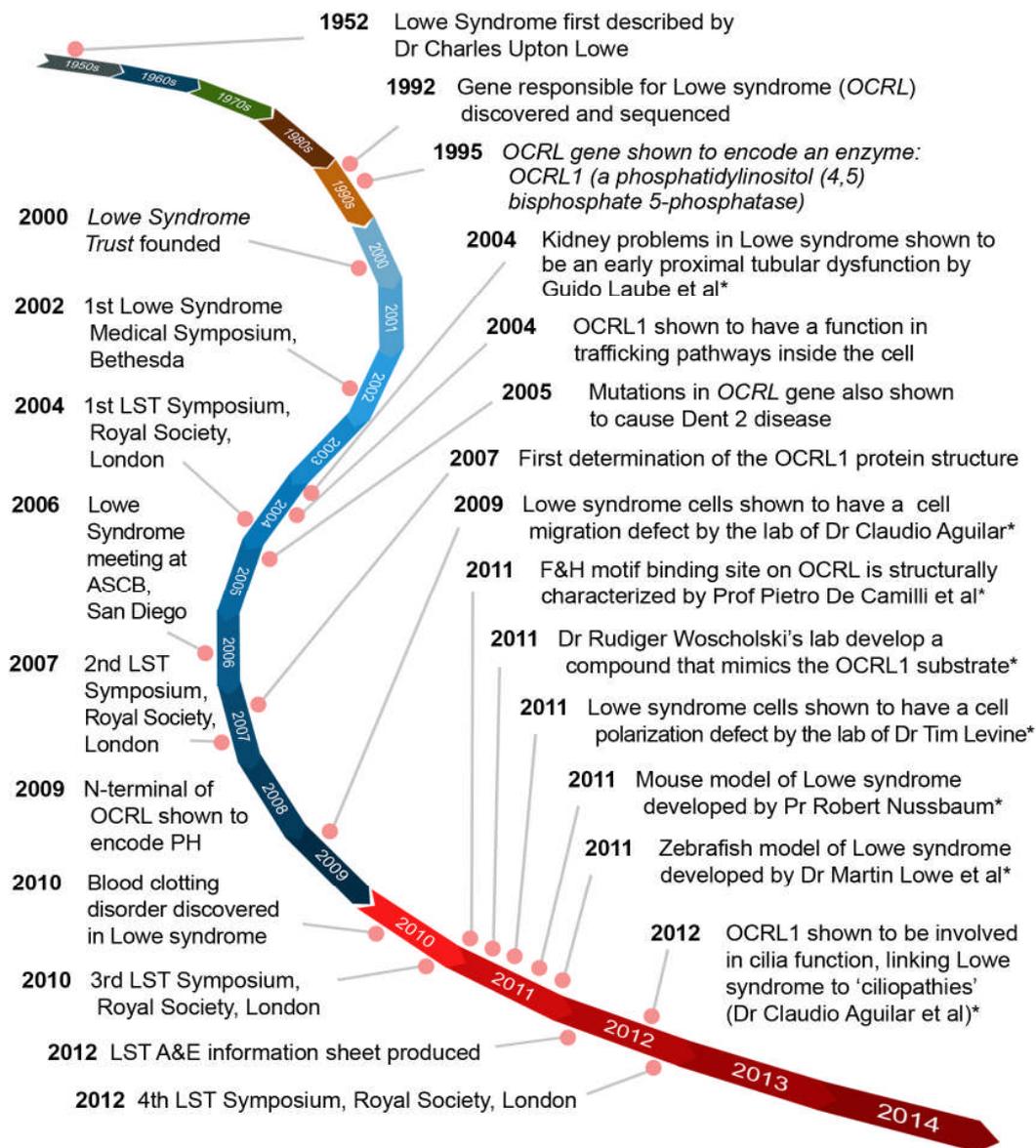
Since the foundation of the *Lowe Syndrome Trust* in 2000 there has been a rapid acceleration in the pace of discovery and research surrounding Lowe syndrome, including many key discoveries.

The *Lowe Syndrome Trust* organizes an International Symposium every two years – an opportunity for researchers to come together to share their work, learn from each other and stimulate future research.

The *Lowe Syndrome Trust* has set up a Scientific Advisory Board comprising expert biomedical researchers who assess research proposals put forward by researchers seeking funds to work on Lowe syndrome.

The following timeline depicts some of these important breakthroughs in Lowe syndrome research and shows the significant increase in our understanding of the disease over the last 15 years.

### Lowe Syndrome Timeline



\* denotes projects funded by grants from the Lowe Syndrome Trust

One research project tends to lead to another as knowledge increases and new areas for investigation are developed. Although there have been dramatic advances in the understanding of Lowe syndrome during the five decades since it was first recognized, there is much that remains a mystery. With advances in medical and scientific technology and with the strong support of the *Lowe Syndrome Trust*, the future will undoubtedly see researchers finding more answers to the many profound and baffling questions that remain. For further details of current research projects, please contact the *Lowe Syndrome Trust*.

There is still much we do not know but given the recent speed of discovery the future of improved care and eventually a cure for Lowe syndrome may be just around the corner.