Understanding Chromosome & Gene Disorders

Urofacial syndrome (UFS) (Ochoa syndrome)

rarechromo.org

This guide is designed to help people with Urofacial syndrome and their families, and the healthcare professionals looking after them. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

What is Urofacial syndrome?

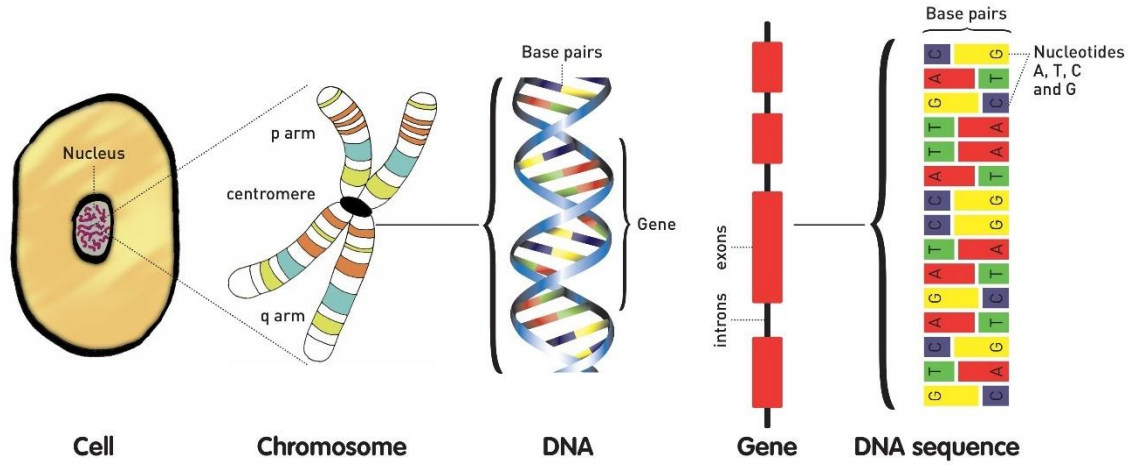
Urofacial syndrome (UFS), also referred to as Ochoa syndrome, was first reported in 1979 and is a rare genetic condition that is characterised by problems with passing urine and emptying the bladder, as well as characteristic facial expressions. Other possible features include problems with bowel function, such as constipation or loss of control of bowel movements, and an inability to fully close the eyelids during sleep. As is common with genetic conditions, each person is affected differently - even among affected members within the same family.

Most people with UFS have been found to have a change in either the *HPSE2* gene or *LRIG2* gene (for some no change in either of these two genes has been found).

What causes UFS?

Genes are instructions that have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies. In people with genetic conditions, one or more of their genes don't instruct the body as we would expect, which can lead to changes in how their body works.

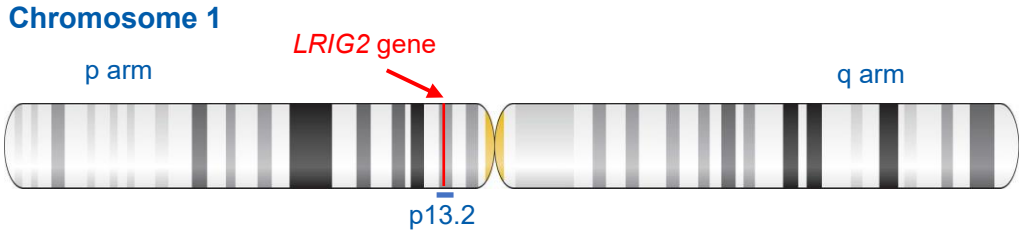
DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long.



UFS has been found to be caused by specific changes (known as pathogenic variants) to the DNA sequence of either the *HPSE2* gene or, less commonly, the *LRIG2* gene.

- The *HPSE2* gene is located in the long 'q' arm of chromosome 10 in a region called 10q24.2 (as shown in the image below).

- The *LRIG2* gene is located in the short 'p' arm of chromosome 1 in a region called 1p13.2 *(*as shown in the image below).



We have two copies of chromosomes 1 and 10 in our cells, so we also have two copies of the *HPSE2* and *LRIG2* genes.

UFS occurs when both copies of either the *HPSE2* gene or the *LRIG2* gene are affected. This is known as autosomal recessive since all numbered chromosomes are called autosomes and genetic conditions that only occur when both copies of an autosomal gene are affected are known as recessive. *Unique* publishes separate guides to Autosomal Recessive Single Gene Disorders and Autosomal Recessive Inheritance.

The *HPSE2* gene sequence is used to make a protein called heparanase 2. This protein is important because it is found in certain nerves that send instructions to parts of the body, including the bladder to control how it works.

The *LRIG2* gene sequence is used to make a transmembrane protein containing leucine-rich repeats and immunoglobulin-like domains. This protein is important because, like heparanase 2, it is found in nerves that send instructions to the bladder to control how it works.

Genetic Report

The results of genetic (genomic) testing are likely to be given to you by your geneticist, a genetic counsellor or a bladder specialist who ordered the test.

An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), which can identify gene variants, is shown on the next page for the *HPSE2* gene.

p.Arg153Ter (R153*) c.457C>T in exon 3 of the HPSE2 gene (NM_021828.4)

p.Arg153Ter (R153*)	Signifies the change to the protein: the amino acid arginine (Arg also called R) has been converted to a stop of protein formation (signified by Ter or *) at position 153 in the sequence of amino acids that make up the protein. This is predicted to lead to an absence of the HPSE2 protein.
C>T	signifies the gene sequence change; the C nucleotide has been replaced by a T nucleotide
c.457	signifies the base pair position of the change within the gene sequence (the position where the C nucleotide has been replaced by the T nucleotide)
exon 3	signifies which part of the gene has been altered, in this case exon 3
HPSE2 gene	signifies the gene that is affected
NM	denotes the reference sequence used.

Unique publishes a separate guide to Interpreting Genetic Test Results.

What features and symptoms do people with UFS have?

As is common with many genetic conditions, children and adults with UFS can have a range of symptoms and features. As more people are diagnosed, and information is shared, the range of symptoms and features, and the likelihood of a child or adult having these features, will become clearer.

Most people are diagnosed in early childhood but those who are more severely affected may be diagnosed prenatally (before birth). Very mildly affected people may only be diagnosed following testing after the diagnosis of a relative.

Development, intellectual abilities and growth are generally unaffected.

Common features

- Characteristic facial expressions (an inverted facial expression)
- Problems with urination, which can lead to difficulty controlling the stream of urine (incontinence), and can result in bedwetting and/or daytime incontinence
- Problems with emptying the bladder (urinary tract dysfunction), which can lead to frequent urinary tract infections (UTIs), a build-up of urine in the kidneys (hydronephrosis) and kidney inflammation (pyelonephritis). If untreated, urine infections can lead to kidney damage.
- Problems with bowel function, including constipation and, less often, loss of control of bowel movements (encopresis)

Other possible features include:

- Incomplete closing of the eyelids during sleep (nocturnal lagophthalmos)
- High blood pressure (hypertension), secondary to kidney damage

Appearance

While the resting facial expression is unaffected, nearly all children and adults with UFS have a characteristic frown-like facial expression when they try to smile or laugh.

This “inverted facial expression” may be noticeable from the time that a baby begins to smile but may not raise any concerns. However, since this feature shows a strong association with anomalies of the urinary tract, where it is observed a thorough and prompt examination of the urinary tract by a specialist doctor is recommended. This could result in an earlier diagnosis of UFS and the features that are associated with this condition, such as urinary tract infections (UTIs). The necessary steps to prevent and/or treat the features of UFS can then be taken at an early stage leading to fewer complications.

Medical concerns

The following medical concerns have been found in people with UFS. Not all children and adults with UFS will be affected in the same way, even where more than one person in a family is affected.

Kidney and urinary tract anomalies

Problems with the urinary system (urinary tract dysfunction) that lead to problems with emptying the bladder are the most common reason for a person with UFS coming to the attention of doctors.

These problems can range from mild to severe and are often first observed in early childhood but features such as an enlarged bladder and/or kidney(s) and ureter(s) (the tube-like structures that carry urine from the kidneys to the bladder) are sometimes observed prenatally in an ultrasound scan.

Due to increased pressure in the bladder, incomplete emptying in children with UFS can lead to a build-up of urine leading to dilatation of the bladder (megacystis), ureters (hydroureter) and kidneys (hydronephrosis). Early signs may include difficulty controlling urination, which can lead to daytime or night-time wetting (incontinence). It can also lead to frequent urinary tract infections (UTIs), which need to be treated with antibiotics. These UTIs may cause no symptoms but can be more serious and be very debilitating and painful. Sometimes a UTI can spread to the bloodstream (urosepsis) and require urgent medical treatment, including with intravenous antibiotics. Rarely, repeated UTIs and the consequences of hydronephrosis can cause the kidneys to become damaged and inflamed, which in the most serious cases can lead to progressive kidney failure.

An early diagnosis and treatment can reduce or potentially prevent damage to the bladder and kidneys, which if left untreated can be severe and irreversible.

Constipation

Constipation, where bowel movements become less frequent and it becomes more difficult to pass a stool, affects about two thirds (2 in 3) of people with UFS. Roughly half of those with constipation will go on to develop a condition in which the failure to have bowel movements causes stools to accumulate in the body, in the colon or rectum. This can lead to the eventual bowel movement occurring involuntarily away from the toilet (encopresis) and may result in soiled underwear.

Eyes

Some people with UFS may not be able to close their eyes completely when they sleep (nocturnal lagophthalmos). This appears to be a relatively common feature of UFS and can lead to poor sleep and the eyes feeling dry upon waking. Further symptoms affecting some can include inflammation of the cornea (keratitis), a scratched cornea (corneal abrasion) and eye infections.

High blood pressure (hypertension)

Some people with UFS may have high blood pressure (hypertension) due to kidney damage. This can be treated with medication to prevent further damage to the kidneys.

Behavioural changes

Behavioural concerns are not a feature of UFS. Nevertheless, urinary symptoms like incontinence can have a major psychological impact on the child living with the condition and for their family members.

Unsurprisingly, children may therefore exhibit a range of emotions depending on their personality and the symptoms they experience, from anxiety and irritability to withdrawing into themselves or acting out. Useful tips and strategies to help the child and the wider family to adjust can be found at eric.org.uk.

How common is UFS?

It is difficult to say. Currently (2024), more than 150 people with UFS have been reported in the medical literature. Males and females are affected in equal numbers. As this is a condition due to changes inherited in a gene from each parent, UFS is more common in families where relatives have children. The condition is under-recognised, and we are working to increase awareness.

Why did this happen?

Gene variants happen naturally and are not due to anyone's diet, environment or lifestyle. We all have our own unique set of gene variants, and most of these DNA changes have no obvious effect. This is often the case for autosomal recessive conditions where a change to one copy of the gene is not expected to cause any symptoms or features, so a parent would be unaware they had it. It is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault.

In most people identified so far (2024) with UFS, each parent passed on a copy of either the *HPSE2* gene or *LRIG2* gene with a variant to their child with the condition. In a small number of children with UFS the genetic change has not been identified.

Can it happen again?

The chance of having another child affected by a rare autosomal recessive gene condition depends on the genetic code of the parents. If both parents are known to carry a UFS-related pathogenic variant, theoretically one child in four (25%) would have UFS, two (50%) would be unaffected carriers (like the parents) and one (25%) would be unaffected and not a carrier. This chance resets for each pregnancy.

All the biological children of a person with UFS will be unaffected carriers of the pathogenic variant inherited from the person with UFS (unless the person with UFS has biological

children with someone who also has UFS or is a carrier of a pathogenic variant for UFS).

Once a person has been diagnosed with UFS, genetic testing can be carried out of relatives who may also carry the UFS-related pathogenic variants identified in the affected person, including siblings of an affected child who should be tested as soon as possible after they are born.

Each family situation is different, and a clinical geneticist or genetic counsellor should be able to give you specific advice for your family.

Unique publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition.

Can UFS be cured?

At present, there is no cure for UFS. However, early diagnosis means that the chance of developing features associated with UFS, such as UTIs or chronic kidney disease, can be reduced or even prevented and the appropriate monitoring and interventions can be put in place. Researchers are developing gene therapy for this condition and so treatment options may change in the future.

Management recommendations

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of UFS that are present in the person who has been diagnosed with UFS should be carried out. This can determine which of the features of UFS are present and how severe they are.

Supportive care

How a person with UFS is cared for is likely to require co-ordinated care by a multidisciplinary team of specialists, including:

Paediatricians - doctors specialising in the physical, mental and social health of children from birth to young adulthood.

Urologists - doctors who specialise in diagnosing and treating conditions affecting the urinary system.

Nephrologists - doctors who specialise in conditions affecting the kidneys.

Surgeons - doctors who are specially trained to perform medical operations.

Ophthalmologists - doctors who specialise in conditions affecting the eyes.

Specialist nurses and/or other healthcare professionals may need to systematically and comprehensively plan an affected child's treatment.

Treatments and therapies

Treatment will depend on the specific features and symptoms experienced by the affected person but may include:

- Therapies for UTIs, which usually include antibiotics for the treatment and prevention of bacterial infections, and pain relievers (analgesics).

- Specific medications may be prescribed such as anti-cholinergic and alpha-1-adrenergic blockers, to help urine flow more easily.
- Some people may benefit from catheterisation (a procedure that uses a flexible tube, called a catheter, to drain the bladder and collect urine).
- Some people may need to undergo surgery to eliminate urinary tract obstruction and reconstruct certain parts of the urinary tract.
- Those with long-term kidney failure may require procedures that regularly remove excess waste products from the blood (dialysis). In rare, severe cases of kidney failure, a kidney transplant may be considered.
- A high-fibre diet or stool softeners and/or laxatives may be recommended to help relieve constipation. Some benefit from enemas when symptoms are particularly severe.
- An ophthalmologist may prescribe lubricant eye drops to use during the day and eye ointment at night for nocturnal lagophthalmos.

Surveillance

It is recommended that the following evaluations are carried out to monitor an individual's existing UFS symptoms, how they respond to care and treatment, and whether any new symptoms emerge over time:

- Ultrasound imaging, to monitor for evidence of urinary tract dysfunction, should be carried out at least once a year throughout childhood.
- Kidney function should be monitored, as per the recommendations of a nephrologist and according to whether there is evidence of kidney disease and disease progression.
- On-going examinations by an ophthalmologist for nocturnal lagophthalmos.
- Assessment for constipation/encopresis at least once a year.

Certain substances that cause damage to the kidneys (nephrotoxic substances), which includes certain drugs and antibiotics, should be avoided if possible.

Is there any research into new treatments for UFS?

Research into improved treatments and management for various features of UFS is ongoing. In addition, although UFS is a relatively rare condition, the *HPSE2* and *LRIG2* genes are the subject of continued research, including the possibility of using gene therapy to correct certain symptoms of UFS. These include recent studies aimed at correcting the urinary tract symptoms of UFS in mice with pathogenic variants in the *HPSE2* gene using gene therapy, which indicated that this may be a viable future therapeutic option to treat the urinary tract symptoms in humans.

Details of clinical trials related to a particular condition or gene can be found at ClinicalTrials.gov and EU Clinical Trials Register.

Sources

The information in this booklet is drawn from the published medical literature and families affected by UFS. The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (https://pubmed.ncbi.nlm.nih.gov/). You can obtain most articles from Unique.

References

*Newman WG (2013) [updated 2023] Urofacial Syndrome. GeneReviews® [Internet]. PMID 23967498. Link to article

*National Organisation for Rare Disorders (NORD) - rarediseases.org/rare-diseases/urofacial-syndrome/ Link to article

*MedlinePlus - medlineplus.gov/genetics/condition/ochoa-syndrome/ Link to article

*Genetics and Rare Diseases Information Center (GARD) - rarediseases.info.nih.gov/diseases/104/index Link to article

Note: an asterisk indicates articles which are “open access” and available to everyone at https://pubmed.ncbi.nlm.nih.gov

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK,
Tel: +44(0)1883 723356
info@rarechromo.org I www.rarechromo.org

Join Unique for family links, information and support.
https://rarechromo.org/join-us/

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at:
https://rarechromo.org/donate/ Please help us to help you!

Websites, Facebook groups and other links:
www.eric.org.uk - ERIC - the children's bowel and bladder charity
www.kidneyresearchuk.org/ - A UK-based kidney research charity

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change.

This guide was written by Unique (CA) and verified by Professor Bill Newman (PhD FRCP FMedSci), Consultant in Clinical Genetics, Manchester University NHS Foundation Trust (MFT) and University of Manchester, UK.

Version 1 (2024)

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 5460413