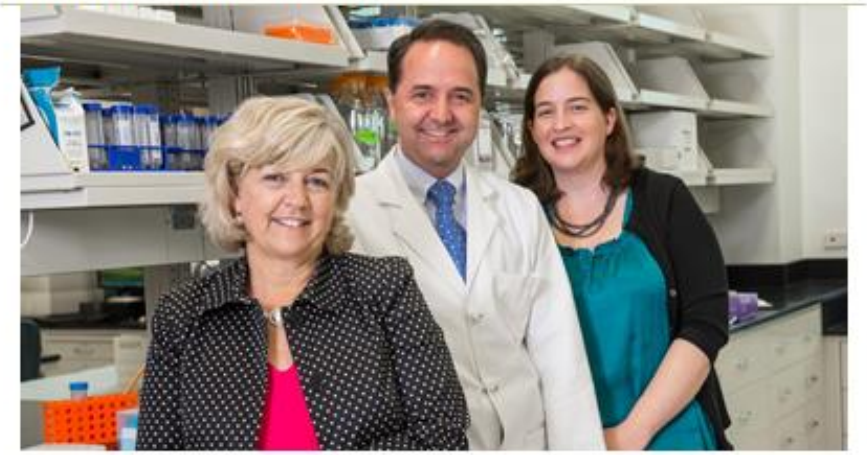
UKD Research Team



Dr. Anthony Bleyer, M.D., M.S. has studied inherited kidney disease for over 15 years, working with doctors and scientists to identify the genetic causes of kidney disease in over 300 families worldwide.

Vicki Robins, R.N., B.S.N. has over 30 years of nursing experience and has been a part of the research team since 2001.

Kendrah Kidd, M.S. has over 10 years of laboratory experience and joined the research team in 2012.

FOR MORE INFORMATION ABOUT UKD:

UKD Foundation® Uromodulin Kidney Disease Research and Support
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AN INTRODUCTION TO

Uromodulin Kidney Disease

Introduction

"Uromodulin kidney disease is a rare inherited kidney disease.

We were part of a scientific research team that identified the genetic cause of Uromodulin kidney disease in 2002.

Since then, our team has been working to identify families that have this condition and to develop a cure.

With patients, doctors and scientists working together, we will find a cure for Uromodulin kidney disease."

-Anthony J. Bleyer, M.D., M.S.

What is Uromodulin Kidney Disease (UKD)?

It is an inherited kidney disease causes slow worsening of kidney function over time and is often accompanied by gout. It is also known as:

- Medullary cystic kidney disease type 2
- Familial juvenile hyperuricemic nephropathy type 1
- Uromodulin associated kidney disease

The goal of this brochure is to educate families about this condition.

This brochure is intended to provide only general information about UKD. It is not intended to, nor does it constitute medical or other advice. Please consult your physician for recommendations specific to your care.

Table of Contents

What is UKD?

UKD Facts:

- Uromodulin Kidney Disease (UKD) is a rare type of inherited kidney disease, meaning it runs in families.
- UKD is found equally in males and females and it does not "skip generations".
- Most individuals with UKD have slow loss of kidney function. As they get older, they may need dialysis or a kidney transplant. The severity of kidney failure and the age of onset can vary within the same family.
- Many individuals with UKD have gout, which is painful but treatable with medication.

Many times, family members will say:

"A lot of my family members have gout and kidney failure."

"Our kidney doctor said we have an inherited kidney disease, but he is not sure of the exact name."

"There is a disease that has run in my family for a long time, but no one knows what it is."

"I have a kidney disease and I am worried if my children have it."

UKD Symptoms

SIGNS AND SYMPTOMS OF UKD

- Strong family history. Most patients have a parent and other family members who have had kidney disease.
- Bedwetting as a child. About 1/3 individuals with UKD have bedwetting, compared to 1/5 children who do not have UKD. This is caused by the kidneys inability to concentrate urine.
- Gout. Not all persons with UKD have gout, but almost every affected family has someone who has had gout. In UKD, the kidney is not able to excrete uric acid efficiently. This causes uric acid levels in the blood to increase and leads to deposits in the joints.
- Blood creatinine levels slowly increase.
- Kidney failure. As one ages, the kidneys are less able to filter waste products, such as creatinine, increase in the blood to the point where individuals begin to feel tired, weak and develop anemia. In most individuals, these symptoms slowly worsen and will require dialysis or a kidney transplant.
- Little protein and no blood in the urine.
- High blood pressure can develop as kidney function worsens.

NOT SIGNS OR SYMPTOMS OF UKD

- Kidney and bladder infections. Individuals with UKD get these infections at the same rate at those without the disease.
- Back pain over the kidneys does not occur.
- Kidney stones are not caused by UKD.

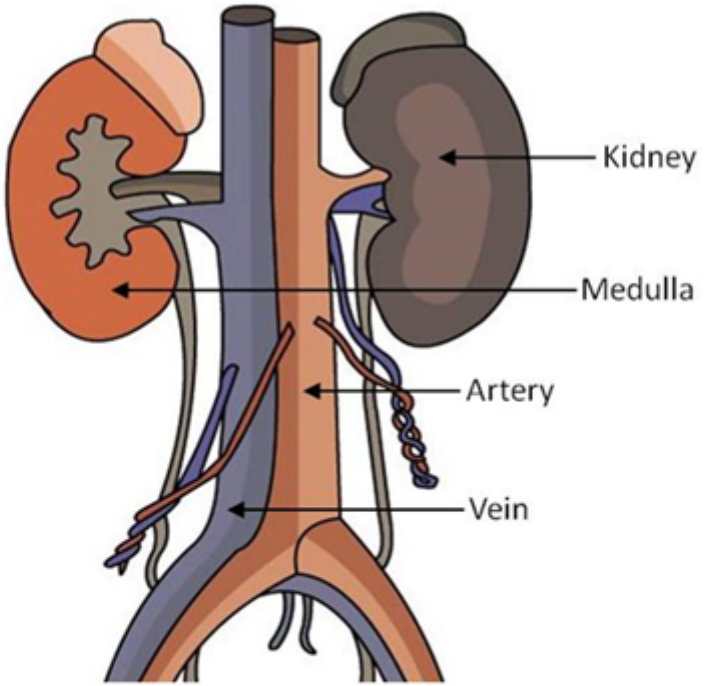
Frequently Asked Questions

Q: What do the kidneys do?

A: The kidneys are bean-shaped organs about the size of a fist. They are located in the back next to the spinal column.

Healthy kidneys filter and clean about 200 quarts (189 liters) of blood every day, removing excess water, minerals and wastes.

The kidneys also produce hormones that make red blood cells and control blood pressure. They make active Vitamin D, which the body uses to keep your bones strong.



Q: What happens to my kidneys if I have UKD?

A: UKD causes scarring of the kidneys (fibrosis), which leads to slow loss of kidney function over time. This means eventually, their kidneys are not able to filter and clean their blood, make red blood cells or produce active Vitamin D.

Q: How does having UKD affect my health over the course of my life? How will it make me feel?

A: The main complication of UKD is gout. Gout is painful, but can be treated.

Another complication is kidney failure. It is important to remember that individuals feel very well and normal until they have lost a significant amount of kidney failure.

When individuals have lost about 60% of their kidney function, they begin to feel more tired and may develop a decreased appetite. When 90% of kidney function is lost, they feel tired, have nausea and usually need dialysis or a kidney transplant.

Q: What is gout?

A: Gout is a type of arthritis (inflammation). It often affects the big toe, foot, ankle and knee. It leads to painful swelling, which is very intense for several days. It is caused by a build up of a chemical called uric acid.

In UKD, gout occurs in men and women in their teens or 20's. Uric acid builds up because it is not removed properly by the kidney. Gout caused by UKD can be treated the same way other forms of gout are treated.

Q: How can I monitor my kidney function?

A: Kidney function is usually determined by a blood test, called a blood creatinine level. This is part of a group of tests that may be done as part of a routine physical or before surgery.

In UKD, blood creatinine levels rise slowly over time as the kidneys become more damaged. Once creatinine rises to a certain level, often about 6 mg/dL (milligrams/deciliter) or about 500 mmol/L (millimoles/liter), treatments such as dialysis are considered.

Q: What can I do for my health if I have UKD?

A: Currently there is no specific treatment for UKD, but there is still a lot you can do to stay healthy:

1. **Do not smoke.** Smoking makes all kidney diseases worse. It also causes hardening of the arteries and lung disease. It is important to stop smoking if you do.
2. **Check your blood pressure regularly.** As kidney disease worsens, blood pressure can increase. This can lead to increased risk of heart disease, stroke and heart attack. If your blood pressure is high, you should get it treated.
3. **Stay in shape and keep weight under control.** Being very overweight can make future transplant surgery difficult.
4. **Visit your kidney doctor regularly.** They will help you manage signs and symptoms of kidney disease and also help you prepare for a kidney transplant, if needed.

Q: What kind of diet should I eat if I have UKD?

A: When kidney disease is mild, you should eat the same heart-healthy diet that is recommended for the general population.

This is a diet with less meat protein. It is not known if such a diet will slow the rate of kidney disease

Q: Can a urine test be used to diagnose UKD?

A: No. A urine test cannot diagnose UKD.

In many types of kidney disease, there is blood and protein in the urine. However, in UKD, there is very little protein or blood in the urine. For this reason, routine urine tests your doctor may order are not good to diagnose UKD.

Currently UKD is only diagnosed using a genetic test.

Q: Is UKD contagious? How do other family members get UKD?

A: UKD is not contagious. It is a genetic disease, meaning it is inherited. It is passed from one generation to the next.

Q: Can I prevent UKD?

A: No. Unfortunately, there is no way to prevent UKD.

Q: How do I tell my family I have UKD?

A: How you choose discuss UKD with your family is a personal decision. Each person will approach it differently depending on their family.

Sharing information with adult family members will allow them to educate themselves to make informed decisions about their lives and medical care.

Some family members will not want to know about the disease, while others are interested. One should be respectful of the wishes of individuals who do not want to know about this condition. They may at a later time want to discuss this with you, or they may want to find information for themselves.

This booklet may be a good place to start when providing information on this condition.

Q: Does kidney transplant cure UKD?

A: Yes. Individuals with UKD make an abnormal protein in their kidneys that gets trapped in their cells. When a kidney transplant is done, the transplanted kidney is normal and does not make the abnormal protein. Therefore, the disease will not develop in it.

Q: I have UKD. Should my children be tested?

A: The decision to test children is difficult. It is a decision that you must make with your family and physician.

At present, there is no specific treatment for UKD, so learning about it at an early age does not change treatment.

When we are in our late teens and 20's, we begin making plans for our lives in terms of where we will live, career aspirations, starting families, etc… Many individuals want to find out at that time if they are affected to help them make informed medical and personal decisions.

Q: At what age will I need dialysis or kidney transplantation?

A: There is a lot of variation as to the age when individuals with UKD might need treatment for kidney failure.

In some families, individuals begin dialysis in their 20's or 30's, while in others they do not begin until their 60's or later. Even within families, some individuals begin dialysis earlier or later than their parents or siblings. We do not know what causes this variation.

Q: If family members wants to donate a kidney to me, should they be tested for UKD?

A: Yes, family members should be tested for the disease before considering kidney donation.

UKD is an inherited disease. Sometimes family members have a mild case of UKD, meaning labs tests may be normal and they do not know they have kidney disease.

If they were to donate a kidney, their kidney would still make the abnormal protein. UKD would not be cured, and eventually that kidney would also lose its function, requiring dialysis or another kidney transplant.

Also, the kidney donor with UKD would only have one kidney remaining that may eventually fail.

Q: How common is UKD?

A: UKD is considered a rare disease. There are about 500 families worldwide that have been identified with this disease.

Q: Why is UKD research important?

A: The goal of our research is to find a cure for UKD. This is our only goal. To find a cure we will need to study the *UMOD* gene and uromodulin protein in both affected and unaffected people. Because there are so few people with UKD, every individual with UKD who takes part in research provides helpful information.

"The goal of our research is to find a cure for UKD. This is our only goal."

Genetics of UKD

Genes store information for making everything in our body. The information that genes store is used to make proteins, which build our kidneys, blood, process the food we eat, etc…

Everyone has small changes in their genes. When one of these changes causes a disease it is called a mutation. A mutation will cause a protein to be made in the wrong way. The protein will not work properly and will cause problems in the body.

For example, imagine that genes are the blueprints for a factory. If there is a mistake in the blueprint, the factory will have a problem. Sometimes the problem is minor and no one may know the problem exists. Other times, the problem is major and the factory is unable to make its products correctly or at all.

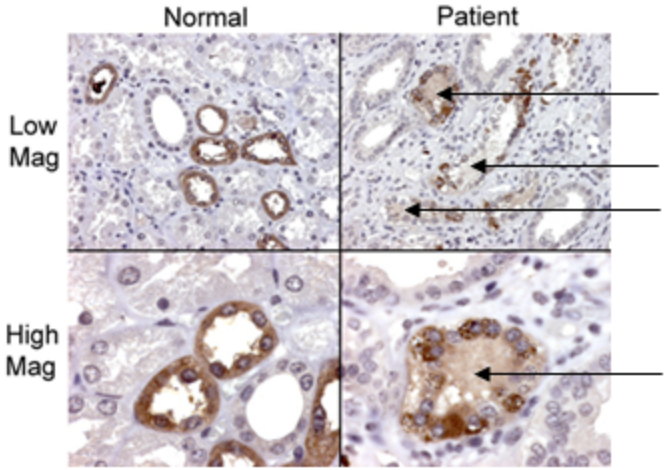
UKD is caused by a mutation in the UMOD gene. Over 50 different UMOD mutations have been found to date.

Uromodulin

UMOD makes the protein uromodulin, also known as Tamm-Horsfall protein. Normally, this protein is excreted by the kidney into the urine. It is the most common protein found in human urine.

In UKD, the abnormal uromodulin is not able to leave the cell. The abnormal protein builds up in kidney cells and even keeps normal uromodulin from being excreted. How it causes kidney failure and gout is still being determined.

The picture below is from a normal person and a person with UKD, this kidney tissue was stained for uromodulin (brown). The normal tissue shows uromodulin present in the tubule cells. In the UKD tissue, the uromodulin deposits abnormally in chunks. These deposits likely cause kidney cell death and lead to kidney failure.



There are many unanswered questions about *UMOD* and UKD, such as:

- What controls the *UMOD* gene?
- How and why does the abnormal uromodulin build up in kidney cells and how does this lead to bedwetting, gout, and kidney failure?
- Why do some patients have mild disease and others have severe disease?

Researching the *UMOD* gene, uromodulin and UKD in patients is the only way forward to finding answers to these questions and finding ways to treat and slow disease progression.

UKD in Families

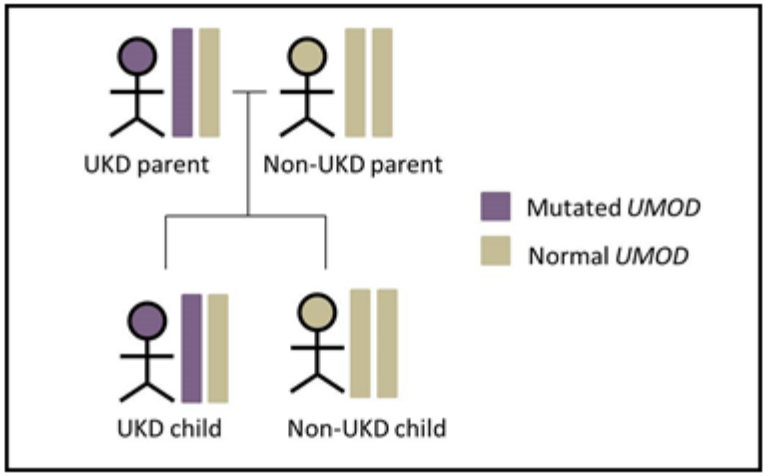
UKD is not contagious. You cannot "catch" UKD, it is an inherited disease. This means that it is passed from one generation to the next by a parent with UKD, such as your father's eyes or your mother's nose.

UKD Inheritance

Everyone has two copies of the *UMOD* gene, one from our mother and one from our father. For individuals with UKD, one of their *UMOD* genes has a mutation. Even though they have a "good copy" as well, it does not stop the abnormal Uromodulin from being made.

When an individual with UKD has a baby, they either pass on the good copy to the child (who will NOT have UKD) or the mutated copy (who will have UKD). It is entirely by chance whether the good or mutated copy is given to the child.

There is a 50% chance that a child of a person with UKD will get the disease. UKD does not skip generations. The medical term for this type of inheritance is autosomal dominant.



If your parents do not have UKD you cannot get it. However, sometimes the UKD is mild and may not be recognized until the blood creatinine levels are checked. Frequently, kidney disease has no symptoms until late in the disease.

Testing for UKD

A genetic test must be performed to find out if an individual has UKD.

It is a blood test. DNA is isolated from the blood and analyzed to determine if a *UMOD* mutation is present. It is not possible to predict the severity of UKD with a genetic test. The genetic test for UKD is a commercially available test from Athena Diagnostics, Inc.

At present, there is not a specific treatment for UKD. Most individuals with UKD will have slowly progressive kidney failure. Some will need dialysis or transplant.

Kidney Transplant

Kidney transplant is a procedure where a surgeon places a new kidney in the lower abdomen and connects the artery and vein of the new kidney to the patient's arteries and veins. Usually the older kidneys do not need to be removed. The new kidney can come from a relative or friend, or from someone who has died and donated their kidneys.

After a transplant, most patients fell healthy again and no longer need dialysis; however, they will need to take medications for the rest of their life to keep their body from rejecting the new kidney.

Individuals with UKD are generally excellent candidates for kidney transplant. This is because UKD only affects the kidney and kidney function is lost gradually, so there is a lot of time to prepare for a transplant.

It is important to stay healthy to be a good candidate for kidney transplant. This includes:

- Having good blood pressure control
- Making sure cholesterol is well controlled
- Exercise and stay fit
- Do not smoke
- Try not to become overweight

It is also important to identify individuals who might be willing to donate a kidney – it can be very hard asking someone to donate a kidney! A donor can be a family member or a friend. If it is a family member, they should also be tested for UKD.

UKD will not come back in the new kidney.
Kidney transplant cures UKD.

If you are interested in kidney transplantation, ask your kidney doctor when it is the right time to be referred for a transplant evaluation.

Dialysis

Dialysis is a procedure that filters an individual's blood to ride the body of harmful wastes, extra minerals and excess fluid. There are two types of dialysis.

Hemodialysis filters blood using a machine as the filter. Most Hemodialysis patients go to a dialysis center for the procedure, though some do it at home.

Peritoneal dialysis is done at home through a catheter that is placed in the abdomen. It can be done at night while the patient is asleep.

Your doctor can help you decide which type of dialysis is best for you, as each type has risks and benefits.

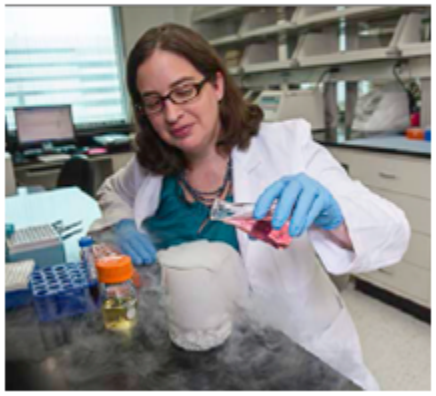
Dialysis is used as a bridge to kidney transplantation.

UKD Research

Our research team is working hard every day with many other doctors and scientists to find a cure or treatment for UKD.

One way we are trying to do this is to study as many individuals with this disease as we can. For example, some individuals do not go on dialysis until late in life, while others go on dialysis when young. Why is there such a difference? We are hoping that by studying the people who have less severe disease, we can find clues that we can use to keep the kidneys working longer.

We often obtain blood and urine samples to study UKD. We work with scientists from all over the world including the First Faculty of Medicine of the Charles University in Prague, the Czech Republic.



UKD as a Rare Disease

In common diseases, there are usually many families that suffer from the disease. It is not hard to find families to study. For example, a researcher will find families right near his medical center to study. Also, some families may be busy and not feel ready to do research. This is usually not a problem because there are so many families that can participate. Research findings will benefit many different families. The government gives a lot of funding for these diseases, so there are many scientists interested in them.

In rare diseases, it is quite the opposite. There are very few families that have a disease. Therefore, doctors studying the disease cannot find families near their medical center to study. Instead, they must work with families from all over the world.

This involves a lot of cooperation between individuals and doctors and shipping of samples.

Also, since there are so few families, the participation of each family is very important. The more families we have, the more we can learn about the disease and factors that make it better or worse. This is ideal for studying diseases from which many people suffer. For rare diseases, even a single family can provide an incredible amount of information.

There are also many fewer doctors studying each rare disease. This is because funding is limited, and most doctors are interested in more common diseases.

Another important factor to consider is that for many diseases, research will help others greatly. For example, a patient taking part in a diabetes study will have little benefit compared to the many diabetic individuals throughout the world who could benefit from a diabetes study. However, with rare diseases, the studies are most likely to benefit those who participate and their families, since the disease is so rare.

For these reasons, the partnership between affected families and the doctors and scientists studying UKD is incredibly important. This research will only be successful if doctors, scientists, and patient families all work together.

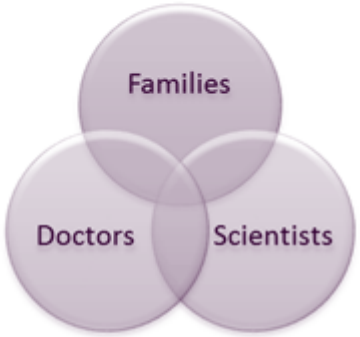
Working Together for UKD

Laboratory research studies *UMOD* and abnormal uromodulin found in UKD to find out how it causes gout and kidney damage. Clinical research works with and studies families affected by UKD. By working together, we can provide education for patients, doctors and scientists about UKD and reach our goal.

The goal of laboratory and clinical research is to find a cure for UKD. This is our only goal.

We encourage any and all questions regarding UKD, *UMOD*, uromodulin and UKD research. We will answer your questions promptly. Please contact Dr. Anthony Bleyer at 336-716-4513 or by e-mail at kidney@wakehealth.edu.

UKD FOUNDATION®



The UKD Foundation® began in 2013 to bring families, doctors and scientists together to provide support, education and develop future treatments.

For more information about the UKD Foundation® please call (828)738-5301, email info@ukdcure.org, or visit www.ukdcure.org

Glossary

Anemia – Anemia caused by kidney disease is when the number of red blood cells circulating in the blood is decreased. Sometimes individuals with anemia need shots to help increase their red blood cell numbers.

Autosomal Dominant – Type of inheritance for UKD where the mutated *UMOD* gene is found on a non-sex chromosome. Dominant means that only one copy of the mutated *UMOD* gene is needed for an individual to have UKD. If you have the disease, each of your children has a 50% chance of getting the disease.

Creatinine – Creatinine is a by-product of muscle metabolism and is removed by the kidneys. When kidneys do not work so well, they do not remove creatinine from the blood. Therefore, the level of creatinine in the blood rises.

Measuring the level of creatinine in the blood is the most common test for checking kidney function.

Gout – Gout is caused when the kidney is not able to filter out a waste product called uric acid. Uric acid then increases in the blood and deposits in joints where it forms crystals. These crystals are painful and lead to inflammation. Typically gout is in the big toe, but it can affect many other joints such as the knees or elbow.

In people who have UKD, gout often develops in teenage males and females. In people who do not have UKD, gout usually develops in males who are in their 40's and 50's, are overweight and often have diabetes.

Women who are pregnant or may become pregnant should not take Allopurinol for gout. Studies have shown that prolonged exposure to Allopurinol during pregnancy can cause birth defects.

High Blood Pressure – High blood pressure is also known as hypertension. Most doctors consider a blood pressure reading greater than about 135/90 to be high blood pressure.