

News About... FSGS Research

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Important Research Update: Gene Implicated in Familial FSGS

A research team at the Duke Center for Human Genetics (CHG) recently identified a gene that causes familial focal and segmental glomerulosclerosis (FSGS).

FSGS is a disease that causes the progressive loss of kidney function, and most affected individuals eventually require dialysis. Other symptoms of FSGS include high blood pressure, protein in the urine, and swelling.



Michelle P. Winn, MD
Principal Investigator

After investigating a large New Zealand family, the FSGS team, led by Dr. Michelle P. Winn, identified the transient potential cation channel 6 (*TRPC6*) gene. *TRPC6* is an ion channel on cell membranes that normally regulates the amount of calcium pumped into a cell. When changed (mutated), this gene causes an increase of calcium into cells. The *TRPC6* gene is the first ion channel associated with FSGS. Previously, genes affecting the cell structure have been found to cause FSGS or other hereditary diseases like FSGS.

The Duke researchers published their findings in *Science* magazine (online in *Science Express*, May 5, 2005; in print 17 June 2005). This genetic discovery will help us to understand

the origin of FSGS and will hopefully aid in finding new and better treatments or even lead to prevention. The advance may also help to identify patients at greatest risk for FSGS before symptoms arise and when therapies might be most effective in slowing disease progression. After a 7-year search, CHG researchers are very excited by this progress; however many years of further study are necessary to identify a possible cure, including investigating how the *TRPC6* gene contributes to FSGS. ❖

Is Testing Available for this Gene?

At this point, it is too early to offer genetic testing for FSGS.

While this finding is exciting and will lead to valuable knowledge about FSGS, it does not yet have a practical use. There is still a lot to learn about the role this gene plays in FSGS. If we, or others, continue to make positive discoveries pertaining to this gene, a clinical test will likely become available. In the event a genetic test is developed, we will notify you, our participants.

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Welcome to News About Familial FSGS Research

This newsletter is published by the Duke Center for Human Genetics (CHG) for the families who participate in our research study on the genetics of Focal Segmental Glomerulosclerosis (FSGS). The CHG includes a team of dedicated researchers looking for genetic and environmental causes of inherited and complex disorders. We hope you will enjoy reading about our recent research progress.

About FSGS

What is FSGS?

Focal Segmental Glomerulosclerosis (FSGS) is a disorder in the blood-filtering parts of the kidney called the glomeruli. *Focal* and *segmental* refer to the pattern of damage to the glomeruli and *glomerulosclerosis* refers to the damage or scarring (*sclerosis*) of the glomerulus. Specifically, *focal* refers to patches within the kidney that are affected and *segmental* indicates that only a portion of the glomerulus is affected.

FSGS damages the glomerulus and allows protein to leak into the urine (proteinuria). Over time, the damage to the kidney may cause kidney failure. FSGS is only one of many causes of kidney failure or end-stage renal disease (ESRD). ESRD affects more than 420,000 patients in the United States with an additional 100,000 new patients diagnosed each year.

What causes FSGS?

The specific cause of FSGS is not well understood. Sometimes FSGS is either associated with--or a result of--another disorder. These secondary causes of FSGS include sickle cell disease, congenital (present at birth) renal (kidney) malformation, obesity, reflux nephropathy, human immunodeficiency virus (HIV), intravenous drug use (e.g., heroin), and certain medications.

How can you tell when someone has FSGS?

When someone is seen in a doctor's office or clinic for suspected renal disease, the urine is tested for the presence of protein (proteinuria). Proteinuria suggests the kidney may be damaged in some way. A healthy glomerulus allows only a very small number of large protein molecules to leak into the urine.

The person may also have nephrotic syndrome, defined by a number of symptoms including:

- low blood protein (hypoalbuminemia)
- high blood pressure (hypertension)
- edema (swelling, usually of the lower legs and feet)
- high blood lipids (hyperlipidemia)
- blood that clots too easily (hypercoagulability)

However, many people with FSGS have only mild nephrotic syndrome or are not affected in this way. Patients with FSGS may also have a progressive loss of renal function, where the damage worsens over time. Eventually, the individual's kidneys cannot properly cleanse waste products from the blood and sufficient volumes of urine cannot be produced. If left untreated, these waste products can become toxic to the body.

What is the treatment for FSGS?

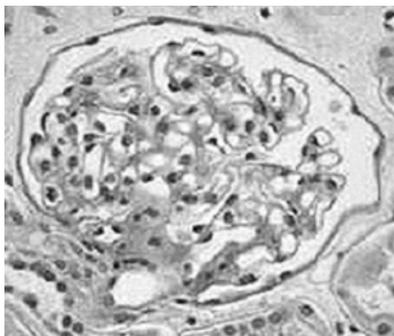
Currently, there is no cure for FSGS. Once the scarring of the glomeruli associated with FSGS has developed, no medication can reverse the damage. FSGS treatment is based on improving symptoms and delaying the progression of FSGS in order to slow the development of ESRD. Symptoms most notable for requiring treatment include proteinuria and a diagnosis of nephrotic syndrome. Oral steroids, such as prednisone, are commonly used to treat FSGS. These steroids can produce partial or complete remission (lack of symptoms) in about 30-50% of patients with FSGS. In some patients, proteinuria may be treated with drugs called angiotensin-converting enzyme inhibitors (ACE-I). These ACE-I drugs are blood pressure medications that also decrease the amount of protein excreted in the urine. Other medications are in the testing process. Patients with FSGS, in coordination with their nephrologist, should carefully consider their best plan of treatment.

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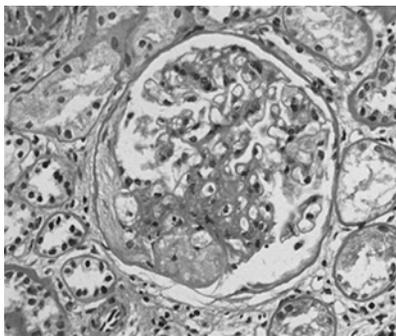
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Can FSGS be inherited?

Yes, FSGS can be inherited. For the past 25 years, it has been observed that in some families more than one member is diagnosed with FSGS. This tendency is *familial aggregation* and it indicates there is an inherited or genetic component to FSGS. Specifically, FSGS is considered an autosomal dominant disorder meaning that the disorder is caused by a change (mutation) in a gene (see "*What is a Gene?*" on page 4). If a parent has the gene that causes FSGS, then each of his or her children has a 50% chance of inheriting this gene. In our present study, we are interested in studying the familial form of FSGS. ❖



Normal Glomerulus



**Segmentally Sclerotic
Glomerulus**

Meet the FSGS Researchers

A project of this magnitude requires the efforts of many individuals. Experienced CHG researchers, with the help of interested families, continue the search for the genes that cause familial FSGS.

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Sources of Information and Support

National Kidney Foundation

30 East 33rd St, Ste 1100
New York, NY 10016
Phone: (800) 622-9010
Phone: (212) 889-2210
Fax: (212) 689-9261
E-mail: info@kidney.org
<http://www.kidney.org/>

American Kidney Fund

6110 Executive Blvd, Ste 1010
Rockville, MD 20852
Phone: (800) 638-8299
E-mail: helpline@akfinc.org
<http://www.akfinc.org/>

American Association of Kidney Patients (AAKP)

3505 E. Frontage Rd, Ste 315
Tampa, FL 33607
Phone: (800) 749-2257
Fax: 813-636-8122
E-mail: info@aakp.org
<http://www.aakp.org/>

Introduction to Genetics

What is a Gene?

Genes are very small structures inside almost every cell of the body. Genes are the instructions that tell our body how to grow and develop. Humans have approximately 40,000 genes. Genes come in pairs and are made of strands of genetic material called deoxyribonucleic acid, or DNA. Genes line up similar to beads on a string to form larger structures called chromosomes. Genetic disorders are caused by changes in genes that prevent the gene from performing its proper function.



What is a Chromosome?

Like genes, chromosomes come in pairs. Each cell in our body has 23 pairs of chromosomes (for a total of 46); one member of each pair is inherited from the mother and the other from the father. The first 22 pairs (numbered 1 through 22) are called autosomes. The last pair are called the sex chromosomes because they determine if we are male or female. Females have two X chromosomes and males have one X chromosome and one Y chromosome.

How Do We Find Genes that Contribute to Familial FSGS?

Following is a description of the two strategies we use to identify the genes that contribute to Familial FSGS that we hope you will find helpful in understanding the research your participation supports.

Genome Screen and Linkage Analysis

Genome screens and linkage analysis have been very successful in discovering the genes that cause many genetic disorders. Advances in laboratory and computer technology have now made this approach possible for genetic disorders like FSGS. The genome comprises all of a human's genetic material. A genomic screen consists of DNA laboratory studies and a statistical analysis called linkage analysis. Linkage analysis is the first step towards finding a gene. Looking for the genes that cause a genetic disorder is similar to locating someone's house without knowing the exact address. By narrowing down the area you are searching in (from state to city to street), eventually you can find the address of a particular person. Just as gas stations or restaurants can be used as landmarks when locating a friend's house, scientists use markers to find a gene. The instructions encoded in genes are written in a special genetic alphabet consisting of four letters – A, T, C, and G (called nucleotide bases). These bases are the critical chemicals from which DNA is made. The sequence (order

in which these letters occur) tells the body how to make certain proteins. Markers are the small sequences of DNA along the chromosomes that may differ slightly from individual to individual. These differences (called polymorphisms) do not usually affect a person's health, but can be easily identified and used to look for genes. Linkage analysis is performed by testing many different markers on all the chromosomes, trying to find markers that are consistently found in family members who have FSGS, but are not found in family members without FSGS. These markers are used as landmarks to identify exactly which chromosome a gene causing a disorder is located on (like which street a house is on). Certain statistical methods can tell scientists how close these landmarks are to a gene. If a marker is believed to lie very close to a gene, then the marker is "linked" to the gene. This is why we call this DNA analysis "linkage analysis."

Candidate Gene Analysis

Candidate genes are genes scientists know something about, such as their exact location on a particular chromosome and their function. Candidate genes for FSGS may be genes known to be involved in the glomerulus or podocyte, specific structures that are known to be altered (or abnormal) in FSGS. Thus, the function of candidate genes "make sense" for possibly being involved in the biology of kidney disease; these genes are good "candidates" for being related to the development of FSGS. Candidate

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gene analysis for FSGS involves studying the potential candidate gene in individuals with FSGS to see if the gene has a genetic change (mutation) that is not seen in the genes of individuals who do not have FSGS. If genetic changes in candidate genes are identified, then it is possible the candidate gene contributes to the development of FSGS in humans. Just like the genomic screen and linkage analysis, it is a laborious process and often takes many months to a year to thoroughly study just one candidate gene.

A Combined Strategy is Most Successful

Our laboratory strategy is to study candidate genes in families in which only many individuals have FSGS. Once a particular piece of a chromosome is identified as being linked through the genomic screen, we try to study candidate genes located on that particular piece of the chromosome. This combined strategy helps narrow down the potential candidate genes we choose to study because it allows us to choose candidate genes located in the area of interest discovered by the genome screen. We use databases, developed in part by the Human Genome Project, to identify which genes are located on a particular piece of a chromosome. We then study these potential candidate genes to determine if they truly are related to FSGS. As a result, this genomic screen and linkage analysis give us the street on which an individual's

house is located. Candidate gene analysis is like knocking on the door of a house on that street, in search of a particular individual. Our laboratory has been successful discovering the genes that contribute to the development of other complex disorders.

The Genetics of Complex Disorders

Some disorders are determined by changes in more than one gene. Complex disorders (cystic fibrosis, sickle cell anemia, or hemophilia, for example) do not follow a predicted pattern of inheritance as is seen in other rarer genetic disorders caused by a change (mutation) in only one gene. In some instances, changes in the genes that contribute to complex disorders must be in combination with certain environmental factors, such as exposure to certain chemicals, medications, or diet. This type of inheritance is often referred to as multifactorial, or "complex," because many different, genetic and/or environmental factors are involved. A person will have a complex disorder if he or she has the right combination of changed genes and environmental exposures.

Sometimes the genes that contribute to complex disorders are called *susceptibility genes* because they make a person susceptible to developing the disorder after exposure to specific environmental factors, but they do not cause the disorder alone. The close relatives of someone with a complex disorder have a

higher chance of developing the disorder than the close relatives of someone who does not have the disorder. Diabetes, heart disease, autism, Alzheimer disease, neural tube defects, Parkinson disease, and many cancer syndromes are examples of disorders that can be caused by multifactorial or complex inheritance. FSGS is an example of a disorder which has complex inheritance. ❖





FSGS Publications

Publication of research findings in peer-reviewed scientific journals is one way to measure progress in research. The efforts of everyone, most importantly the families, will enable us to unravel the genetics of FSGS. Recent publications include:

Winn MP, Conlon PJ, Lynn KL, Farrington MK, Creazzo T, Hawkins AF, Daskalakis N, Kwan SY, Ebersviller S, Burchette JL, Pericak-Vance MA, Howell DN, Vance JM, Rosenberg PB. *A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis.* Science, 5 May 2005; 308:1801.

Stafford-Smith M, Jpodgoreanu M, Swaminathan M, Phillips-Bute B, Mathew JP, Hauser EH, Winn MP, Milano C, Nielson DM, Smith M, Morris R, Newman MF, SchWinn DA. *Association of genetic polymorphisms with risk of renal injury after coronary bypass graft surgery.* American Journal of Kidney Disease, Vol 45, No. 3 (March) 2005; pp. 519-530.

Winn MP. *Approach to the evaluation of heritable diseases and update on familial focal segmental glomerulosclerosis.* Nephrology Dialysis Transplantation. 18 [Suppl 6]: vi14-vi20, 2003.

Neary JJ, Conlon PJ, Croke D, Dorman A, Keoghan M, Zhang FY, Vance JM, Pericak Vance MA, Scott WK, Winn MP. *Linkage of a Gene Causing Familial Membranoproliferative Glomerulonephritis Type III to Chromosome 1.* J Am Soc Nephrol 13: 2052-2057, 2002.

Winn, MP. *Not all in the family: Mutations of podocin in sporadic steroid resistant nephrotic syndrome.* Journal of the American Society of Nephrology, 13:577- 579, 2002.

Neary JJ, Conlon PJ, Croke D, Dorman A, Keoghan M, Zhang FY, Vance JM, Pericak-Vance MA, Scott WK, Winn MP. *Linkage of a Gene Causing Familial Membranoproliferative Glomerulonephritis Type III to Chromosome 1.* J Am Soc Nephrol 13: 2052-2057, 2002.



Please Update Us

We are beginning to update the family history and medical information on families in our study. A member of our research staff may be contacting you in the coming months to obtain updated information about members of your family, to collect medical records, or to finish collecting blood samples from family members. Please keep us in mind when important changes happen in your family. We like to ensure that all of our family trees and mailing lists are accurate. We would like to know if there are any major changes in the health status of family members, such as someone diagnosed with a new medical disorder, if another family member is diagnosed with focal segmental glomerulosclerosis, or if there are new members of your family. Please give us your updates by calling us toll-free at (800) DUKE-CHG or by calling (919) 660-0038.

A Warm Thank You to All Families!

We are indebted to all the individuals and family members who have so generously agreed to participate in this on-going genetic research study for FSGS. Each individual and each family that participates helps the pieces of this research puzzle fall into place. The research described in this newsletter is only possible because of the many individuals and family members who agree to participate. We look forward to continuing to work with all of you over the next few years. Together, we will move closer to our common goal of understanding why and how FSGS develops. We also want to thank all of the families who have helped spread the word about our research. We have received many phone calls and e-mails from families who learned about the study through other families already enrolled in the study. Please keep telling other families about the study, as we continue to enroll additional interested families.

How Can You Contact Us?

We can be reached at
Center for Human Genetics,
Duke University Medical Center Box 3445
Durham, NC 27710

Phone: (800) DUKE-CHG
Phone: (919) 660-0038
Fax: (919) 684-0920
E-mail: fsgs@chg.duhs.duke.edu
Web: <http://www.chg.duke.edu/diseases/fsgs.html>

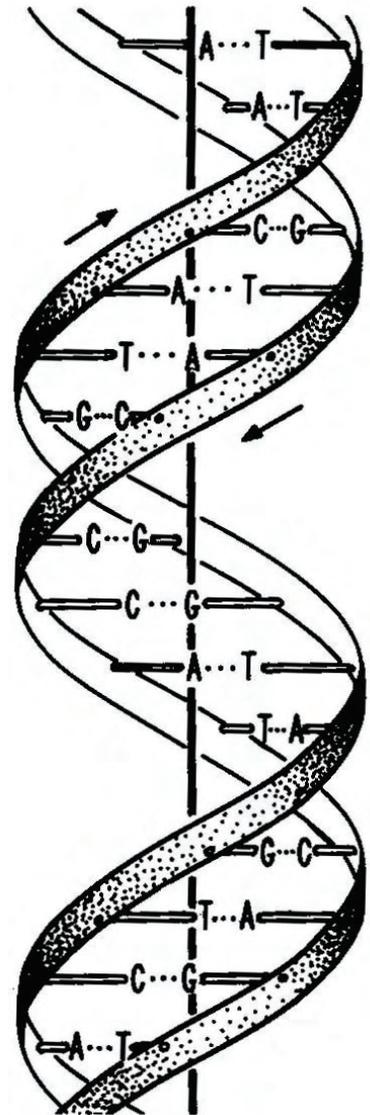
How Else You Can Help

This groundbreaking FSGS research was made possible through both federal grant support and gifts made by individual donors who provide us with the resources necessary to gather essential data from patients. Donors contribute to the purchase of cutting-edge equipment and the development of new technologies. They support innovative research. In fact, individual gifts, large and small, provide an important source of non-government support. Even modest donations, when merged together, create a significant resource for the support of our research, teaching, and patient care.

To make a gift to FSGS Genetics research at the Center for Human Genetics, please call (800) DUKE-CHG, or visit us online at <http://www.chg.duke.edu/giving>.

Gifts can be mailed to: Duke Center for Human Genetics FSGS Genetics Research, DUMC Box 3445, Durham, NC 27710.

Thank You!





Questions and Answers

We speak to many families about participating in research studies. Here are some of the frequently asked questions:

Q: What is involved in FSGS study participation?

A: The first step in joining a genetic research study is to talk with one of the researchers about your family history. Typically, family history information can be obtained during a telephone interview. Depending on the family history, we may request blood samples from several family members, including individuals with and without FSGS. In many cases, a brief physical examination is done on family members willing to participate in the study in order to confirm who does and does not have FSGS. We may request permission to review the medical records of family members who have FSGS.

Q: How will you obtain a blood sample from my family?

A: In some cases, we will travel to your home or other agreed-upon meeting place to obtain blood samples and complete the paperwork or examinations needed for the study. Another option is a mailer kit, which we send to you. It contains blood tubes and instructions that you can take to your local health care provider or laboratory to have blood drawn. Once the blood is drawn, these kits are mailed by an overnight delivery service or the US Post Office directly to Duke University Medical Center at no charge to the family. Participation through the mail will, in most instances, require that we obtain copies of a person's medical records.

Q: How long will the study take?

A: Genetic research studies take many years to complete because we must gather information and blood samples from many different families, run many experiments in the laboratory, and analyze the results. Once a gene is found, it may require even more time to understand its function and/or to develop any treatment based on that understanding. Through our newsletters, we will keep you updated of our progress. The more families

that participate in our study, the faster we will be able to find answers. If you know other interested families with FSGS or if you have other family members who were not able to participate earlier but may be interested in participating now, please have them contact us toll-free at (800) DUKE-CHG or at (919) 660-0038.

Q: Will my family get results from the study?

A: We are not able to give families their specific research results because a specific test for FSGS is not available. Developing such tests is one of the ultimate goals of the study. If a research breakthrough is made and such a test becomes available, families who participated in the research will be given information on how to pursue such testing, if they are interested. In the meantime, this newsletter will provide you and your family with updates on research progress.

Q: Is there any cost to my family to participate in the study?

A: No, we do not charge families for participating in our study. We cover the costs of physical examinations and blood draws by our research staff. If a physical examination by our research staff discovers any abnormalities that require medical follow-up, these expenses would not be covered by the research project.

Q: Who may participate in the study?

A: Any person with a family history FSGS and his or her family members who are willing to participate.

Q: Will my family's medical history be kept confidential?

A: All person and family medical history shared with the research center is kept strictly confidential. Individuals who participate in the research are assigned a unique number in order to protect their identities. Only authorized researchers directly involved in the study can access the research records and family medical histories.

