SickKids | Genome Diagnostics

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a histopathologic finding in nephrotic syndrome in children and adults characterized by excessive urine protein excretion (proteinuria), generalized or isolated swelling of the body tissues (edema), decreased blood protein levels (hypoalbuminemia), and elevated blood lipid levels (hyperlipidemia). FSGS frequently progresses to end-stage renal disease (ESRD), requiring renal replacement therapy in the form of dialysis or kidney transplantation.

Genetics

FSGS can be either primary, due to genetic mutations or secondary, the result of other conditions. The primary form has been observed in both sporadic cases and in patients with a family history of FSGS. The five genes primarily involved in FSGS are listed. FSGS is associated with both an autosomal recessive and autosomal dominant pattern of inheritance. Mutations in the genes *TRPC6* and *ACTN4* account for the dominant forms of FSGS, and only one copy of either gene is required for an individual to be affected. The recessive form is present when a child receives two copies of a defective *NPHS1* or *NPHS2* gene. Mutations in the *CD2AP* gene have shown both autosomal dominant and recessive inheritance patterns.

Gene	Chromosomal Location	Protein
NPHS1	19q13.1	Nephrin
NPHS2	1q25.2	Podocin
TRPC6	11q22.1	Transient receptor potential cation channel 6
ACTN4	19q13	Alpha-actinin-4
CD2AP	6p12	CD2-associated protein

Who Should be Tested?

- Individuals clinically suspected of being affected with FSGS
- Individuals with a family history of FSGS, to determine carrier status
- Pregnancies at risk due to family history of FSGS

Test Methods

- Complete sequencing of the coding region and flanking exon/intron boundaries of the listed genes to identify point mutations.

Test Sensitivity

Mutations in the *NPHS2*, *TRPC6*, *ACTN4* and *CD2AP* genes account for ~50% of FSGS cases.

A nonsense mutation at amino acid 1109 and deletion of nucleotides 121 and 122 in *NPSH1* account for ~90% mutations in FSGS patients from Finland. Other mutations have been described worldwide.

Potential Outcomes & Interpretation of Test Results

Gene	Gene Mutation Found	Explanation
ACTN4 or TRPC6	None detected	This result does not support a diagnosis of FSGS
	One mutation detected	This result supports a diagnosis of FSGS
NPHS1 or NPHS2	None or one mutation detected	This result does not support a diagnosis of FSGS
	Two mutations detected	This result supports a diagnosis of FSGS
CD2AP	None detected	This result does not support a diagnosis of FSGS
	One mutation detected	This result may support a diagnosis of FSGS
	Two mutations detected	This result may support a diagnosis of FSGS

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/

- FSGS1 # 603278
- FSGS2 # 603965
- FSGS3 # 604241

National Kidney Foundation http://www.kidney.org/

Kidney Foundation of Canada http://www.kidney.on.ca/

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations in these genes. A negative result does not rule out the possibility that the individual carries a rare NPHS1, NPHS2, TRPC6, ACTN4 or CD2AP gene mutation not detected by this assay.

2. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

3. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.