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.

**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**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Mutation Found</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTN4 or TRPC6</td>
<td>None detected</td>
<td>This result does not support a diagnosis of FSGS</td>
</tr>
<tr>
<td></td>
<td>One mutation detected</td>
<td>This result supports a diagnosis of FSGS</td>
</tr>
<tr>
<td>NPHS1 or NPHS2</td>
<td>None or one mutation detected</td>
<td>This result does not support a diagnosis of FSGS</td>
</tr>
<tr>
<td></td>
<td>Two mutations detected</td>
<td>This result supports a diagnosis of FSGS</td>
</tr>
<tr>
<td>CD2AP</td>
<td>None detected</td>
<td>This result does not support a diagnosis of FSGS</td>
</tr>
<tr>
<td></td>
<td>One mutation detected</td>
<td>This result may support a diagnosis of FSGS</td>
</tr>
<tr>
<td></td>
<td>Two mutations detected</td>
<td>This result may support a diagnosis of FSGS</td>
</tr>
</tbody>
</table>

For More Information

- 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](http://www.cagc-accg.ca) or the National Society of Genetic Counsellors website at [www.nsgc.org](http://www.nsgc.org)

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.