Genetic Mutations Play a Role in FSGS

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Many advances have been made in understanding the genetics behind focal segmental glomerulosclerosis (FSGS). However, more research is needed to identify additional susceptibility genes and, more importantly, to understand the underlying pathophysiology of FSGS. Andrey S. Shaw, MD, Washington University School of Medicine, St. Louis, Missouri, USA, discussed familial FSGS in the first Michelle Winn Endowed Lecture. The cause of familial FSGS may be a mutation or genetic variants in multiple genes, as well as a combination of genetic and environmental factors. A landmark publication demonstrated that a dominant missense mutation in the TRPC6 cation channel could result in familial FSGS, and also shed light on calcium signaling as a potential underlying mechanism of FSGS [Winn MP et al. *Science.* 2005]. Currently, known genes contribute up to 30% of familial FSGS cases, and Dr Shaw questioned why so many genes are potentially involved in familial FSGS.

In healthy individuals, tens of thousands of podocytes are shed in the urine each day and, under normal conditions, this podocyte loss does not pose a problem, as most individuals are born with about 1 billion podocytes. However, podocytes either have a low replicative rate or cannot divide; therefore, a genetic abnormality that increases the loss of podocytes will lead to glomerular insufficiency. Conditions that affect podocytes include impairment of the cytoskeletal integrity, decreased cell survival or increased apoptosis, and increased podocyte sensitivity to drugs, toxins, cell stress, or other effectors.

A majority of the FSGS research has focused on the familial form of the disease. Dr Shaw and his collaborators turned their attention to the possibility that susceptibility genes exist for sporadic FSGS. Participants in a study of sporadic FSGS cases and controls with Northern European ancestry were evaluated for genetic variants, which included sequencing of all of the known FSGS risk genes plus an additional 2500 genes that are expressed by podocytes. There was a greater number of rare deleterious variants in known FSGS disease genes in sporadic FSGS cases compared with controls (OR, 7.5; $P < 10 \times 10^{-14}$; Table 1). In addition, common and rare variants were found in about 20 genes, of which WNK4, KANK1, and ARHGEF17 were validated using an animal model.

Many genes that were identified play a role in the regulation of the protein actin, are involved in the basement membrane or slit diaphragm, or are transcription factors. Actin appears to be important for kidney function, as a decrease in actin results in effacement of the podocyte foot process.

Dr Shaw concluded that it is not yet clear how the identification of susceptibility genes will contribute to determining the underlying mechanism of FSGS. However, new treatment approaches of FSGS may be uncovered through currently known and newly identified susceptibility genes.

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Table 1. Top 10 Candidate Genes From Different Pooled Association Tests for Focal Segmental Glomerulosclerosis

Burden Test	Variable Threshold Test	C-α Test
DLG5	COL4A4	XYLT1
COL4A4	DLG5	APOL1
WNK4	WNK4	KAT2B
NID1	GCC1	WNK4
EPHX1	EPHX1	BPTF
GCC1	XYLT1	TBC1D9B
XYLT1	IL36G	IL36G
EPHB6	ZFPM2	NXN
APOL1	NID1	ARFGEF1
LAMB1	APOL1	DOCK4

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