

## TRPC6 mutations and Nephrotic Syndrome

In 2005, our knowledge of the genetics associated with FSGS expanded with the publication of an article in the journal *Science* with the discovery of a mutation in the gene TRPC6, encoding a calcium ion channel. Mutations in the channel, located on the cell membrane of podocytes (specialized cells in the kidneys involved in filtration), were found to result in an aggressive form of FSGS in adults. This was an interesting discovery by Dr. Michelle Winn particularly because it provided an alternative explanation for development of FSGS than was previously known<sup>1</sup>. Since its discovery a great deal of research has focused on elucidating the role of mutations in TRPC6 and FSGS.

Until recently, seven different mutations in TRPC6 were identified as a cause of FSGS in adults. In a study from Heeringa and colleagues yet another mutation in the TRPC6 gene was found that leads to early onset FSGS, affecting children as early as nine years of age. This data came after the group analyzed 550 families with steroid resistant nephrotic syndrome worldwide. The researchers found that the mutation discovered led to an aggressive form of FSGS in these children<sup>2</sup>.

The mutation in the channel is called a gain of function mutation because it causes an increase in calcium into the cell but the mechanism behind the mutation and the development of FSGS are still a mystery. Possible explanations provided are that the mutant TRPC6 may affect interactions with the podocyte proteins leading to abnormalities or they may amplify injuries present. In a study by researchers in Boston, the interactions of TRPC6 have been evaluated, and they have identified SNF8 as a regulator of TRPC6, suggesting that modulating this interaction can influence the ability of the TRPC6 mutations to cause FSGS<sup>4</sup>.

To further determine the role of TRPC6 channels, researchers have begun to examine its function and how that is affected when the gene is mutated. Calcium influx into podocytes has been described previously in response to signaling by other compounds (Angiotensin II), but the channels responsible for the influx of calcium were unknown. A study by Dr. Jacobo and colleagues determined that TRPC6 appears to be the elusive calcium channel in the podocyte and thus it likely plays a role in podocyte injury. This observation suggests that maintenance of calcium balance may be critical, since loss of channel activity may have deleterious effects on the specialized cells of the kidney<sup>6</sup>.



While researchers do not yet know exactly how these mutations result in disease, there are a number of talented scientists trying to elucidate the role of TRPC6 in FSGS. As research continues there is hope that these mutations can be a potential target of therapy for FSGS patients to ameliorate the disease.

1. Winn MP, Conlon PJ, Lynn KL, et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. *Science* 2005;
2. Heeringa SF, Möller CC, Du J, Yue L, Hinkes B, Chernin G, Vlangos CN, Hoyer PF, Reiser J, Hildebrandt F. A novel TRPC6 mutation that causes childhood FSGS. *PLoS One*. 2009 Nov 10; 4(11):e7771.
3. N Mukerji, TV Damodaran, MP Winn, TRPC6 and FSGS: The latest TRP channelopathy. *Kidney International* **76**, 1225–1238 (1 December 2009)
4. Johannes S. Schlondorff, Robert Carrasquillo, Anna Greka, Martin R. Pollak **SNF8**, a Component of the ESCRT-II Complex, Binds and Regulates Wild-Type and FSGS-Associated Mutant TRPC6. Presented at the American Society of Nephrology conference in San Diego, October 29 through November 1, 2009.
5. Jason J. Eckel, Nirvan Mukerji, Peter Lavin, Naila Ferimazova, Rasheed Gbadegesin, Tirupapuliur Damodaran, Brandy Bowling, Guanghong Wu, Alison Homstad, Laura Barisoni, Bartlomiej Bartkowiak, Michelle P. Winn Medicine, TRPC6 Deficiency Does Not Cause Glomerulosclerosis. Presented at the American Society of Nephrology conference in San Diego, October 29 through November 1, 2009
6. Sarah M. P. Jacobo, David Billing, Wen Chih Chiang, Arnolt Ramos, Dequan Tian, Jochen Reiser, Hsiang-Hao Hsu, Hermann Pavenstaedt, Anna Greka, TRPC6 Channel Signaling in Response to Angiotensin II Type 1 Receptors Is Essential for the Preservation of the Podocyte Cytoskeleton. Presented at the American Society of Nephrology conference in San Diego, October 29 through November 1, 2009.
7. Rasheed A. Gbadegesin, T. V. Damodaran, Alison Homstad, Bartlomej Bartkowiak, Brandy Bowling, Guanhong Wu, Peter Lavin, Jason Eckel, Nirvan Mukerji, Michelle Winn, TRPC6 Gene Deficiency Ameliorates the Course of Puromycin Induced Kidney Injury. Presented at the American Society of Nephrology conference in San Diego, October 29 through November 1, 2009.
8. Tom Nijenhuis, Joost Hoenderop, Jan Flesche, Harry van Goor, Marinka Bakker, Rene Bindels, Gerjan Navis, Jack Wetzels, Jo Berden, Jochen Reiser, Johan van der Vlag, Angiotensin II-Mediated Upregulation of TRPC6 Expression Via Calcineurin/NFAT Signalling in Podocyte Injury. Presented at the American Society of Nephrology conference in San Diego, October 29 through November 1, 2009.

