## New Insights into TMA

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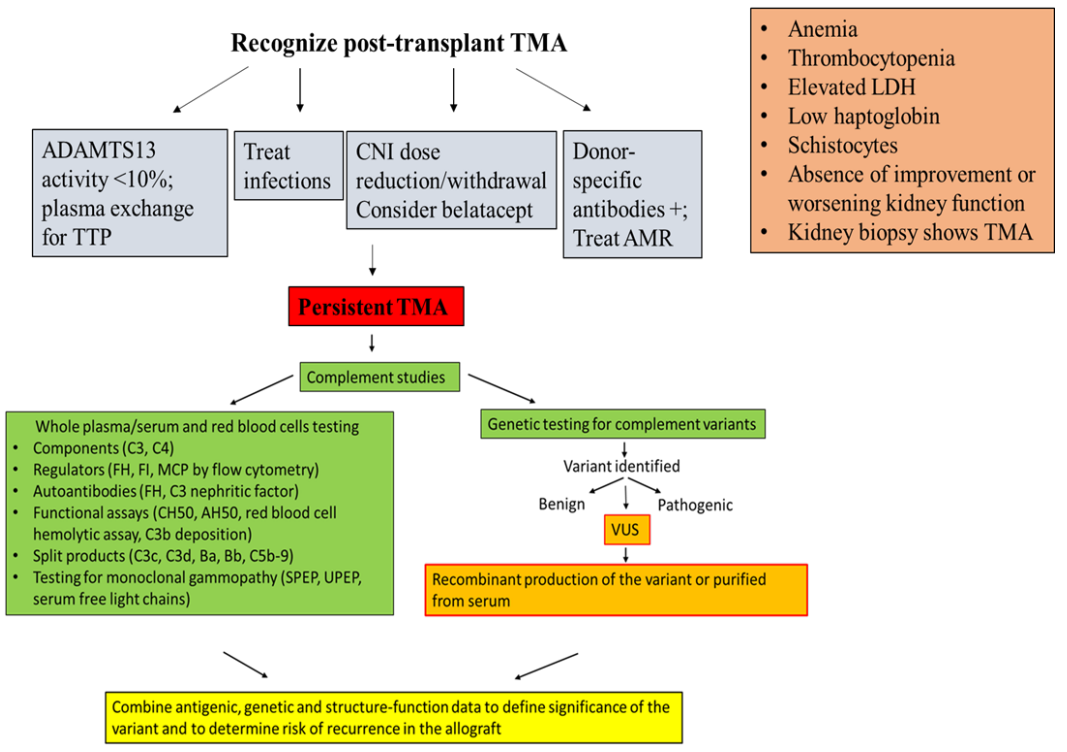
**Figure 2. Approach to diagnosis of posttransplant TMA**




ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TTP, thrombotic thrombocytopenic purpura; CNI, calcineurin inhibitor; AMR, antibody-mediated rejection; LDH, lactate dehydrogenase; FH, factor H; FI, factor I; MCP, membrane cofactor protein; CH50, total complement hemolytic assay; AH50, alternative pathway hemolytic activity; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; VUS, variant of uncertain significance. Reprinted from Ren et al. (16).

# Focal Segmental Glomerulosclerosis Recurrence Posttransplant: It Takes Two to TANGO

By Frank Hullekes, Ruchâma Verhoeff, Paolo Cravedi, and Leonardo V. Riella

Focal segmental glomerulosclerosis (FSGS) recurrence post-transplantation represents one of the most challenging conditions causing kidney allograft failure. Despite intensive research over the past decades, many gaps remain in understanding its pathophysiology. Herein, we review several questions highlighting recent advancements and their potential use in clinical practice.

### Are there any reliable predictors of FSGS recurrence?

FSGS is not a specific disease entity but a histopathological "pattern of injury" seen on light microscopy that primarily targets podocytes. Multiple underlying etiologies that lead to podocyte loss have been identified, including systemic, genetic, and medication induced and those mediated by adaptive kidney responses (Figure 1).

Systemic FSGS is thought to be mediated by a still-elusive circulating factor, inducing podocyte injury and cytoskeleton disorganization, which ultimately leads to proteinuria. The existence of permeability factor(s) is supported by multiple observations: early-onset recurrence after kidney transplantation; resolution of podocyte injury if a kidney transplant is retransplanted in another recipient (1), and remission after plasmapheresis (2). The estimated FSGS recurrence rate is 30% to 60% and represents a major risk for graft loss (3). FSGS recurrence can manifest within hours to days after transplant, in contrast to other glomerular diseases such as immunoglobulin (Ig)A nephropathy, which may recur years posttransplant (3, 4) (Figure 2). Several risk factors are associated with recurrent FSGS: older age at native kidney disease onset, White race, native kidney nephrectomy, and short duration of native kidney disease (<3 years) (3, 5). It has been estimated that recurrent FSGS patients have a hazard ratio for graft failure of 4.8 (95% confidence interval, 2.9–12.2) compared with patients without recurrence (3). Available treatment options for recurrence often fail to achieve remission (2, 3, 6).

Although the potential circulating factor(s) driving systemic FSGS have not been clearly identified, reports indicate a role of anti-nephrin autoantibodies in damaging podocytes (8). Investigators found anti-nephrin autoantibodies in 18 of 62 (29%) patients with minimal change disease (MCD), a condition thought to represent an early stage of FSGS. In a subset of MCD patients, anti-nephrin autoantibody levels correlated with disease activity. Anti-nephrin autoantibodies were also elevated in a case of FSGS recurrence at the time of disease onset. After successful treatment with plasmapheresis and rituximab, the patient achieved remission of proteinuria, associated with the disappearance of anti-nephrin autoantibodies. A recent report from Japan identified a patient with early FSGS recurrence with circulating anti-nephrin autoantibodies at time of recurrence and evidence of punctuate IgG deposits at the 1-hour post-perfusion graft biopsy that co-localized with nephrin (9). Although more research is needed, anti-nephrin autoantibodies may represent a useful biomarker of FSGS disease activity. Quantification of anti-nephrin autoantibodies could allow for risk stratification of FSGS recurrence before transplantation in a subset of patients.

### Does genetic testing help predict the risk of FSGS recurrence?

More than 50 different pathogenic mutations affecting the podocyte or glomerular basement membrane (GBM) have been described in FSGS patients. Mutations in podocyte-related genes include *NPHS1*, *NPHS2*, *TRPC6*, and *INF2*, whereas GBM-related genes include *COL4A3/A4/A5* (10). Genetic FSGS is frequently overlooked because there are no distinctive clinical or histopathological features. When 662 adult patients with familial or sporadic FSGS were analyzed, 30% carried mutations associated with genetic FSGS (11).

The risk of recurrence is low in patients with genetic FSGS (12). A unique genetic form of FSGS is related to the *apolipoprotein L1* (*APOL1*) gene that disproportionally affects patients of Black race. A high-risk *APOL1* genotype is present in approximately 75% of patients with FSGS of Black race (13). Patients with *APOL1*-related FSGS have a low risk of recurrence, likely related to the intrinsic pathogenic role of *APOL1* variants in kidney tissue. Transplant recipients who received a kidney from a donor carrying two *APOL1* high-risk alleles have an increased risk of allograft failure (14). One important exception is a specific mutation in *NPHS1* (nephrin gene), mostly found in Finland. This condition recurs in 25% to 34% of the grafts of patients, driven primarily by the emergence of antibodies against the non-mutated donor nephrin (15).

As a result of widespread availability of genetic panels, it has become easier to diagnose genetic FSGS. The importance of identifying genetic mutations cannot be underestimated for guiding treatment and family counseling. It is important even in cases with advanced kidney failure, as this allows for stratification of a potential recurrence risk post-transplantation.

## How can we further advance our understanding of glomerular disease recurrence post-transplantation?

Although posttransplant FSGS recurrence is a major cause of allograft failure, its relative low incidence and heterogeneity pose major challenges to research. Large registries are needed to achieve insight into disease patterns to identify genetic risk factors. In 2017, we established the TANGO (Post-Transplant Glomerular Diseases) Consortium, a multi-phase collaborative project involving retrospective and prospective study initiatives using patient data and biological samples to better characterize glomerular disease recurrence post-transplant. So far, two major studies have been published on FSGS and IgA recurrence post-transplantation with over 1500 patients recruited (3, 4). The multi-phase approach will set the foundation for a shared international biorepository of samples from glomerular disease patients. All patients diagnosed with FSGS and other glomerular diseases across the United States are invited to participate in the TANGO Consortium's currently ongoing prospective observational studies, aiming to gain better insight into glomerular disease recurrence and its associated risk factors, including anti-nephrin autoantibody levels.

Overall, there is an urgent need to investigate predictors, disease activity biomarkers, pathogenic mechanisms, and response to novel treatments. This necessitates large-scale collaborations among physicians, scientists, funding agencies, industry partners, and patients to redefine and optimize transplant care for glomerular disease patients: It takes two to TANGO! ■

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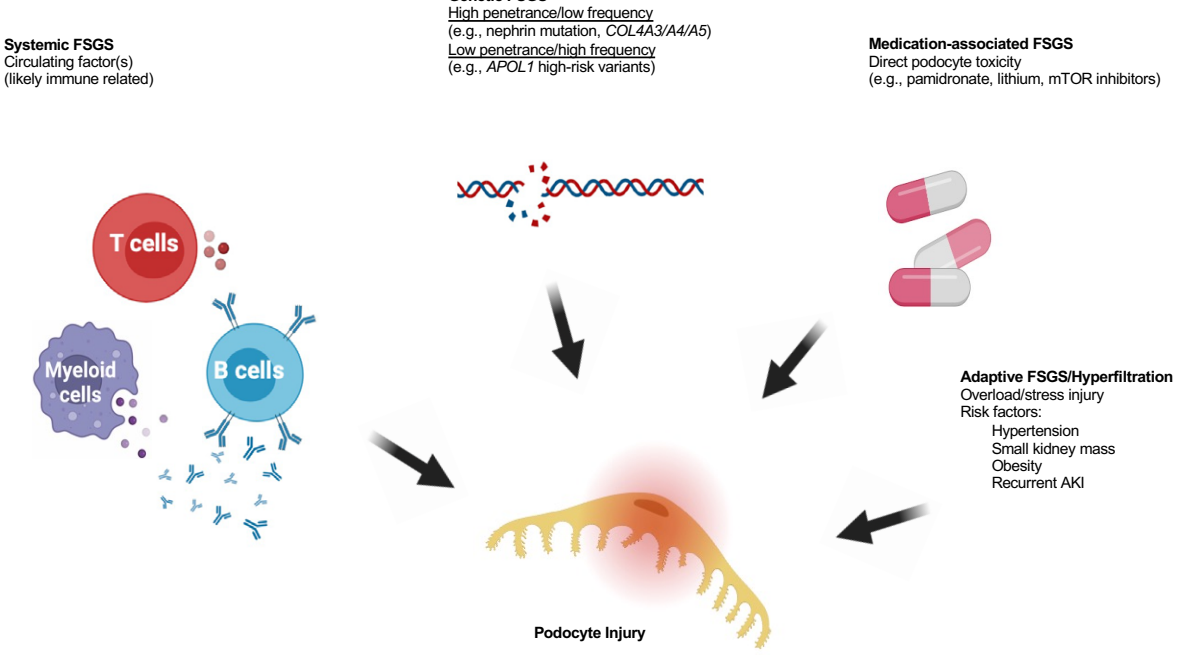
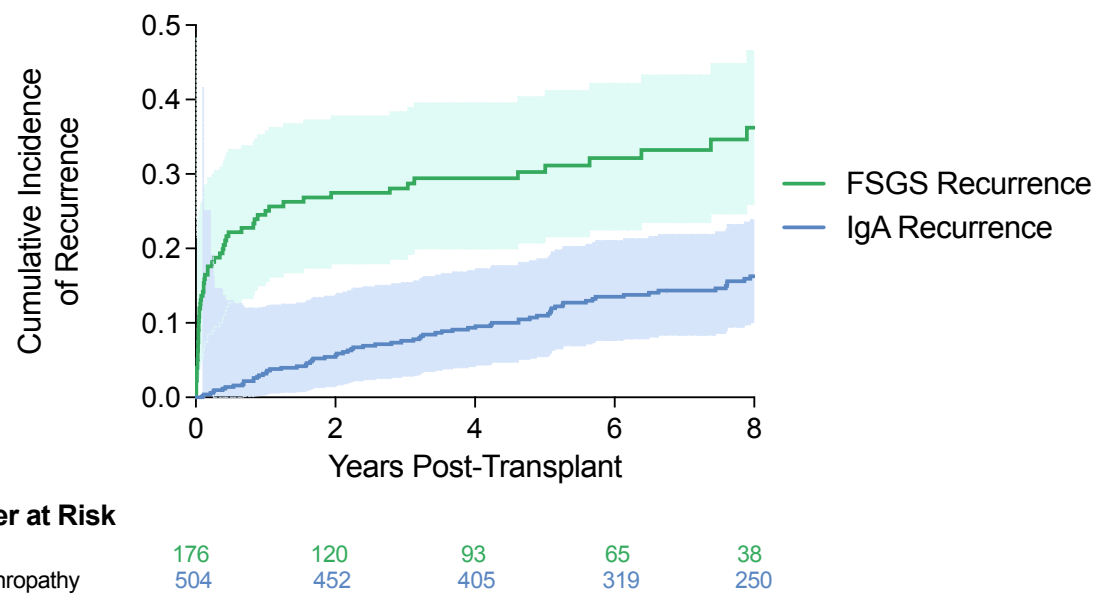
**Figure 1. Underlying etiologies for the podocytopathy in FSGS patients**




AKI, acute kidney injury; mTOR, mammalian target of rapamycin. Created with BioRender.com.

**Figure 2. Cumulative incidence of recurrent FSGS and IgA nephropathy post-transplantation**

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