

Submission No. : PN01-0001

Session Title : Pediatric Nephrology 1

Session Topic : Pediatric Nephrotic Syndrome

Date & Time, Place : June 14 (Fri) / 17:00-18:30 / Room 4 (201)

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## **Pathogenesis of Pediatric Nephrotic Syndrome**

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NEPHROTIC syndrome (NS) is the most common chronic glomerular disease in children, with various immunological mechanisms suggested to be involved in its pathogenesis, although its precise etiology remains unknown. Genome-wide association studies (GWAS) including Japanese pediatric steroid-sensitive NS patients revealed that the HLA class II gene and NPHS1, which encodes nephrin are susceptibility genes for the disease (J Am Soc Nephrol 2018, Kidney Int 2020). Furthermore, subsequent international GWAS meta-analyses revealed that NPHS1 is a susceptibility gene specific to East Asian populations (Nat Commun 2023). RECENTLY, Watts et al. from Harvard University reported that 29% of patients with minimal change NS, including adults, had anti-nephrin antibodies (J Am Soc Nephrol 2022). In collaboration with Harvard University, we measured paired anti-nephrin antibodies in 14 Japanese pediatric NS patients during active disease and remission. We found that 50% were positive for anti-nephrin antibodies, which significantly decreased or disappeared during remission (Ped Neph 2023). ADDITIONALLY, we developed antibodies for dual staining of IgG and nephrin protein on frozen renal biopsy specimens, and found frequent and specific co-localization in nephrotic syndrome patients. This finding is consistent with the results of circulating anti-nephrin antibodies, suggesting a high likelihood that IgG co-localized with nephrin in renal tissue are anti-nephrin antibodies. HOWEVER, many questions remain unanswered, including the prevalence of anti-nephrin antibodies in NS patients, their correlation with disease activity and treatment response, and their relationship with genetic factors like HLA class II and NPHS1 genotypes. Collaborative research across multiple institutions in Japan aims to address these gaps, potentially leading to revised disease concepts, tailored treatment strategies based on genetic information, and a deeper understanding of NS pathophysiology.

**Keywords:** nephrotic syndrome, anti-nephrin antibody, minimal change, FSGS, NPHS1