

EMBARGOED FOR RELEASE until June 14, 2018 – 5:00 PM (ET)

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STUDY UNCOVERS NEW INFORMATION CONCERNING CHILDHOOD KIDNEY DISEASE

Findings could lead to improved treatments.

Highlights

- Researchers have identified genetic variants linked to an increased risk of developing nephrotic syndrome, a pediatric kidney disease.
- The variants are found in genomic regions involved in regulation of the immune response.

Washington, DC (June 14, 2018) —New research provides insights into the genetics underlying a debilitating kidney disease in children. The findings, which appear in an upcoming issue of the *Journal of the American Society of Nephrology (JASN)*, could lead to new diagnostics and, ultimately, treatments.

Although nephrotic syndrome (NS) is rare, with an incidence of 2–7 patients per 100,000 children, it is the most common glomerular disorder of childhood, and it causes failure of the kidney's filtration barrier to retain protein in the bloodstream. Massive amounts of protein are then lost in the urine, including important clotting factors and antibodies to fight infection. Steroids and other immunomodulatory treatments are given to try to halt disease progression to chronic kidney disease and kidney failure, but these medications are nonspecific and their side effects are significant.

Current clinical classifications of NS are descriptive, based on the kidney's appearance under the microscope or the patient's response to steroids. A more precise molecular understanding of NS is needed to develop targeted and effective care for patients.

To examine the genomic underpinnings of NS, a team led by Pierre Ronco, MD, PhD (INSERM, Sorbonne University and Assistance Publique-Hôpitaux de Paris, in France) analyzed the genomes of nearly 400 children with the condition in France (NEPHROVIR cohort), Italy, and Spain, followed by nearly 100 additional children in North America enrolled in the NEPTUNE cohort. "Our primary goal in this research was to discover genetic variants associated with increased risk of pediatric NS. Our secondary goal was to elucidate clinical and molecular correlates of any risk alleles that we found," said Dr. Ronco.

The team discovered that genetic variants in 3 regions within the human leukocyte antigen (HLA) region of the genome were associated with pediatric NS in Europe. Analyses of North American children with NS of diverse microscopic forms conducted by Matthew G. Sampson, MD, MSCE (University of Michigan School of Medicine, Ann Arbor, Michigan) revealed that these variants are associated with a significantly increased likelihood of experiencing complete remission. Across both continents, children with NS harboring these risk variants were significantly younger at the age of disease onset. Finally, 2 of these risk variants were associated with decreased expression of specific HLA genes within the kidney's filtration barrier in patients with NS. (HLA genes code for proteins that are responsible for the regulation of the immune system.)

"It is remarkable that all risk variants that we have identified are associated with other immune-mediated diseases, which strongly support underlying immune dysregulation in NS," said Dr. Ronco. "Also, these robust discoveries suggest that as we continue to increase our sample sizes for genome-wide association studies in pediatric forms of NS, we should continue to identify additional risk variants."

Study co-authors include Hanna Debiec, Ph.D., Claire Dossier, M.D., Eric Letouzé, Ph.D., Christopher E. Gillies, Ph.D., Marina Vivarelli, M.D., Rosemary K. Putler, MS, Elisabet Ars, M.D., Ph.D., Evelyne Jacqz-Aigrain, M.D., Ph.D., Valéry Elie, Ph.D., Manuela Colucci, Ph.D., Stéphanie Debette, M.D., Ph.D., Philippe Amouyel, M.D., Ph.D., Siham C. Elalaoui, M.D., Abdelaziz Sefiani, M.D., Ph.D., Valérie Dubois, M.D., Tabassome Simon, Ph.D., Matthias Kretzler, MD, PhD, Jose Ballarin, M.D., Francesco Emma, M.D., Matthew G. Sampson, MD, MSCE, and Georges Deschênes, M.D., Ph.D.

Disclosures: No financial disclosure related to this study. This study was funded by grants to Pierre Ronco from the European Research Council ERC-2012-ADG_20120314 (Grant Agreement 322947) and the Agence Nationale pour la Recherche (ANR "Genetransnephrose" ANR-16-CE17-004-01). Matt Sampson is supported by the Charles Woodson Clinical Research Fund and by National Institutes of Health RO1-DK108805. The Nephrotic Syndrome Study Network Consortium (NEPTUNE), U54-DK-083912, is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. RDCRN is an initiative of ORDR, NCATS. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCure Kidney International, and the Halpin Foundation. The French NEPHROVIR cohort has been supported by 2 grants of the "Programme Hospitalier de Recherche Clinique" PHRC 2007-AOM07018 and PHRC 2011-AOM11002. The Nephrovir network is coordinated by the Pediatric Nephrology Unit of Robert-Debré Hospital, the "Unité de Recherche Clinique de l'Est Parisien" and the "Délégation de la Recherche Clinique de la Région Ile-de-France".

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Italian investigators from Rome are supported by the Associazione per la Cura del bambino Nefropatico ONLUS.

The article, entitled "Transethnic, Genome-Wide Analysis Reveals Immune- Related Risk Alleles and Phenotypic Correlates in Pediatric Steroid-Sensitive Nephrotic Syndrome," will appear online at <http://jasn.asnjournals.org/> on June 14, 2018, doi: 10.2215/ASN.2017111185.

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Matt Sampson Pediatrics Department's information department would like to promote this story.

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