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Researchers identify the types of genetic mutations associated with nephrotic syndrome

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A study being conducted at the Federal University of São Paulo (UNIFESP), São Paulo State, Brazil, assembles efforts in clinical and basic research on childhood nephrotic syndrome, focusing on kidney transplant patients. The aim is to identify the genetic mutation profile associated with the disease and thereby facilitate early diagnosis, providing a foundation for more accurate medical decisions and enhancing family counseling.

Initial findings from the research, which is part of a Thematic Project supported by the Sao Paulo Research Foundation - FAPESP, have been published in the journal *Transplantation*. The study features in an editorial Commentary published in the same issue of the journal, highlighting unique clinical characteristics, such as the decision to analyze only children who reached end-stage renal disease from nephrotic syndrome and required a transplant.

Nephrotic syndrome is the second most frequent cause of chronic kidney disease in children. It is usually treated with corticosteroid drugs, but 15% of treated children do not respond to this type of drug. These cases may progress to chronic or end-stage kidney failure, requiring dialysis or transplantation.

"The percentage may not seem high, but the consequences can be devastating. In 40% of transplanted children there's a possibility of renal

graft loss due to relapse. In renal retransplants, relapse is practically certain, making these patients dependent on dialysis to survive," said Luciana Feltran, a pediatric nephrologist at UNIFESP and first author of the article.

Steroid resistance is known to be genetic in origin in some cases, making the identification of mutations crucial to diagnosing and treating these patients appropriately.

Feltran and research groups at UNIFESP's Medical School (Escola Paulista de Medicina, EPM) led by Paulo Koch and João Bosco Pesquero, principal investigator for the Thematic Project supported by FAPESP, sequenced 24 genes associated with nephrotic syndrome using next-generation sequencing (NGS). Samples were taken from 95 patients who had received a kidney transplant before reaching 19 years of age. Congenital cases, in which symptoms appeared before the child was 3 months old, were excluded.

The researchers identified 149 variants in 22 of the sequenced genes, classifying them as pathogenic (5), likely pathogenic (20), likely benign (80), and benign (44). No variants of genes PDSS2 and LMX1B were found. NPHS2 was the most common mutated gene.

"We found that nephrotic syndrome was of genetic origin [hereditary or via mutation] for eight patients [8.4%] and probably of genetic origin for five others [5.2%]. The numbers match global data for areas where parental consanguinity is not high, such as Europe and the United States," Feltran explained.

The gene APOL1 was analyzed separately because it is not typically associated with the appearance of nephrotic syndrome but is significant in progression of the disease to end-stage kidney failure. Considering mutations of APOL1, eight other cases (8.4%) were classified as being

probably of genetic origin.

According to Feltran, it is important to understand in detail what each mutation causes in patients (i.e., the correlation between genotype and phenotype). "For example, if a certain variant causes early-onset nephrotic syndrome that progresses slowly to chronic kidney disease, and bearing in mind that in the scientific literature, no patients with this mutation have ever responded to treatment with corticosteroids, there are no reports of post-transplant relapse, and transmission is recessive, then in this case, we can avoid the use of drugs with many adverse side-effects and plan a transplant with a high probability of success, including consideration of the parents as potential kidney donors," she said.

Without the support of genetics, she added, treatment and transplant preparation are performed "in the dark". All that can be known is that on one hand, the patient may not respond to drug-based therapy, and on the other hand, there is a strong probability of relapse after transplantation. These uncertainties are distressing for families and medical teams alike.

Unique group of patients

The 95 cases covered by the study were followed for at least six months at Hospital Samaritano de São Paulo or UNIFESP's Kidney Hospital. Patient information, including demographics and clinical details, was collected from medical files and verified in interviews with parents.

The data collected included age at nephrotic syndrome onset, time to end-stage kidney failure, occurrence of associated extra-renal abnormalities, family history, kidney biopsy report (if any), date of transplantation, donor type (living or deceased), recurrence of nephrotic syndrome, and graft loss.

The next step consisted of taking patient blood samples for genetic

sequencing, bioinformatics analysis, validation, and statistical analysis.

"The study focused on cases in which the disease was most severe, with loss of kidney function, and for which the history of the syndrome was known. It was an ideal group for analysis of the genotype-phenotype correlation," Feltran said.

This correlation allowed researchers to identify and investigate many of the proteins involved in the glomerular filtration barrier, which malfunctions in both genetic and non-genetic forms of nephrotic syndrome. This information will be useful in the future to help find more effective treatments for the disease.

"Because São Paulo receives patients who are referred from various parts of Brazil to have kidney transplants there," Feltran explained. "With only two hospitals, we obtained a larger number of cases than many international multicenter studies."

National network

The results obtained in the study of children with transplants will soon be part of a national network for the diagnosis of childhood nephrotic syndrome.

"The idea is that the Thematic Project will give rise to a center capable of building bridges like this between clinical and basic research, especially in molecular biology and genetics," Pesquero said.

The launch of the Brazilian Childhood Nephrotic Syndrome Network (ReBraSNI) is scheduled for the next Brazilian Pediatric Nephrology Conference, which will be held in Curitiba, Paraná, in April 2018.

"We want to attract other Brazilian researchers in pediatric nephrology

and construct a facility not just in terms of structure and services but above all for research collaboration," Pesquero said.

More information: Luciana S. Feltran et al, Targeted Next-Generation Sequencing in Brazilian Children With Nephrotic Syndrome Submitted to Renal Transplant, *Transplantation* (2017). DOI: 10.1097/TP.0000000000001846

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