

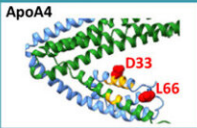
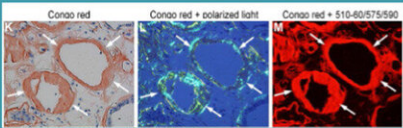
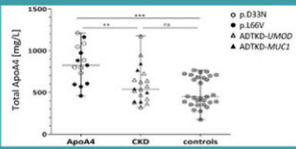
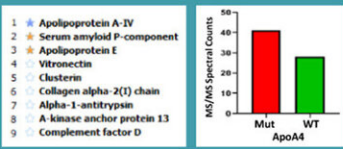


Scientists identify mutations that cause inherited kidney disease

January 22 2024

Autosomal dominant ApoA4 mutations present as tubulointerstitial kidney disease with medullary amyloidosis.

<p>Cohort</p> <ul style="list-style-type: none"> Genetically unresolved ADTKD families <p>Methods</p> <ul style="list-style-type: none"> Genetic analyses <ul style="list-style-type: none"> WGS WES Sanger seq Microscopy <ul style="list-style-type: none"> Light Fluorescent Electron Proteomics <ul style="list-style-type: none"> Kidney Plasma 	<p>Outcomes</p> <ul style="list-style-type: none"> 5 families with APOA4 mutations <ul style="list-style-type: none"> 2 families p.D33N 3 families p.L66V 48 genetically affected 14 genetically unaffected <p>APOA4 phenotype</p> <ul style="list-style-type: none"> Autosomal dominant Bland urinalysis Chronic kidney disease Mean age of ESKD: 64.5±11.3 years Elevated plasma ApoA4 	<p>Outcomes</p> <ul style="list-style-type: none"> Mutations located in an amyloidogenic region of ApoA4 Amyloid deposits exclusively located in renal medulla of probands <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>ApoA4</p> </div> <div style="text-align: center;">  </div> </div> <ul style="list-style-type: none"> Elevated plasma ApoA4 in genetically affected individuals Mutated ApoA4 is the most abundant protein in amyloid deposits. <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;">  </div> <div style="width: 45%;">  </div> </div>
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Krnchova, et al. 2023

CONCLUSION

Autosomal dominant ApoA4 mutations can cause tubulointerstitial kidney disease with medullary amyloidosis.

Credit: *Kidney International* (2023). DOI: 10.1016/j.kint.2023.11.021

Genetic changes or mutations can cause hereditary kidney disease, which can eventually lead to dialysis or the need for kidney transplantation. Identifying the cause of inherited kidney disease is the first step in identifying a treatment.

With that goal in mind, researchers at Wake Forest University School of

Medicine and the First Faculty of Medicine of Charles University in Prague, Czech Republic, have discovered a new genetic cause of inherited [kidney disease](#).

The findings were recently [published](#) in *Kidney International*.

According to Anthony J. Bleyer, M.D., professor of nephrology at Wake Forest University School of Medicine and corresponding author of the study, the mutations were found in a gene that encodes a protein involved in lipid transport. The mutations cause the lipoprotein to deposit in the middle (medulla) of the kidney, leading to chronic kidney disease.

Bleyer has studied families with inherited kidney disease for the past 20 years and has collected DNA from more than 500 families. While the genetic cause of kidney disease has been found in most of the families, for some families it remains unresolved.

For the past 10 years, Bleyer has also collaborated closely with Stanislav Kmoch, Ph.D., from the First Faculty of Medicine of Charles University.

"Through our work with Dr. Bleyer and Wake Forest University School of Medicine, we've now identified a total of five different causes of inherited kidney disease that affect thousands of individuals," Kmoch said.

In the present study, the researchers identified a mutation in the APOA4 gene, a gene that encodes the protein APOA4 that carries lipids in the circulation, as a cause of kidney disease in these families.

"We were really surprised that a mutation in a protein carrying lipids would lead to kidney disease," Kmoch said.

For this study, researchers collected DNA samples from a large family from New England. Kmoch compared the DNA of affected family members vs. unaffected family members.

"When we analyzed the DNA, we found a small change in the APOA4 gene that was present in the affected individuals that was not present in the unaffected family members. We were surprised because APOA4 is expressed in the intestinal epithelium and not in the kidney. We then examined the DNA samples from our other unsolved families and found two families that had the same mutation," Kmoch said.

After finding the mutation in one family in New England, Kmoch scanned the Wake Forest registry and found another family in New England with the same mutation, as well as a patient from a family in eastern Canada. Bleyer and Kmoch then began collaborating with Andrew Orr, M.D., a geneticist and associate professor of ophthalmology of the Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, who had extensively characterized the family in eastern Canada. Through [genetic testing](#), the researchers determined that the three families are distantly related.

In addition, there were two other families from the Wake Forest registry that were found to have a different mutation in APOA4. In all five families, [family members](#) who had the change in the APOA4 gene had kidney disease, while those who did not have the mutation did not have kidney disease.

To determine how the APOA4 mutations caused disease, the investigators analyzed protein deposits (amyloid) that were found in the middle of the kidney on previous biopsies from affected individuals.

These deposits were analyzed by scientists led by Nelson Leung, M.D., from the Mayo Clinic in Rochester, Minn., and found to contain the

abnormal APOA4 protein. Computer modeling of the mutated proteins revealed that the [mutations](#) cause the protein to be unstable and prone to agglomeration.

The investigators showed that while the normal APOA4 protein is filtered by the blood and reabsorbed back into the body or excreted in the urine, the mutant protein tends to stick together and deposit in the medulla of the kidney. This slow accumulation of protein leads to slowly progressive [chronic kidney disease](#).

Bleyer also noted that much of the previous work on the structure and function of APOA4 had been carried out by Richard Weinberg, M.D., professor of internal medicine at Wake Forest University School of Medicine,

"Dr. Weinberg studied APOA4 for more than 30 years," Bleyer said. "His help was instrumental in understanding the pathophysiology of this newly identified disease."

The investigators are also interested in seeing whether dietary interventions are effective in lowering the production of the abnormal protein to prevent the progression of kidney disease, but additional research is needed, Bleyer said.

"While inherited kidney disease can lead to the need for dialysis or the need for [kidney transplantation](#), many families do not know the cause," Bleyer said. "We are committed to helping these families."

More information: Tereza Kmochová et al, Autosomal dominant ApoA4 mutations present as tubulointerstitial kidney disease with medullary amyloidosis., *Kidney International* (2023). [DOI: 10.1016/j.kint.2023.11.021](https://doi.org/10.1016/j.kint.2023.11.021)

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