The power of urine to understand genetic variants in the kidney

Nephronophthisis is a rare genetic disorder of the kidney and the most common genetic cause of end stage kidney failure in children. It can be caused by mutations in more than 20 different genes. In the 50% of cases it is not possible to provide a genetic diagnosis, meaninf that the mutation remains unidentified. A genetic diagnosis is very important in order to provide a definitive diagnosis, to prevent the need for a renal biopsy and to perform screening of at risk individuals.

Thanks to next-generation sequencing tools, nowadays it is possible to sequence quickly and relatively cheaply the exome or genome of a person in search of the genetic fault that causes the disease.

However, our genomes are all slightly different from one another and it can be very hard to work out if a particular variant in the genome of a patient is just a harmless characteristic or is the cause of the disease.

This is particularly true for certain types of mutations that are particularly stealthy. One example is represented by the so-called synonymous mutations, where the letter (the nucleotide) in the genome is different, but this doesn't change the meaning of the word (the amino acid residue in the resulting protein). In principle, these mutations are harmless but, in some case, they can affect the way a gene is processed (spliced) before being translated into a protein. In some case, these apparently harmless genome variants can be responsible for life-threatening genetic disorders.

When a mutation of this type is detected in the patients genome and is suspected to be the cause of the disease, it is often necessary to verify if the variant indeed causes the gene to be abnormally processed in the cells of the patient when compared to cells from healthy people. The cells usually used for this test are cells from the blood or from the skin, due to their accessible nature.

In this study, we present two children with clinical features suggestive of nephronophthisis. Sequencing identified a potentially disease-causing synonymous variant in *NPHP3*, one of the genes known to cause this disease. In order to verify if this variant was responsible for the disease, we compared the way the gene was processed in patients blood cells with blood cells from a healthy person, but we did not observe any difference between the patient and the control.

However, often genes are processed in different ways in different organs, so it is not ideal to verify the nature of variants that may be responsible for a kidney disease using blood cells. At the same time, performing a kidney biopsy in order to access kidney cells would represent an extremely invasive procedure, which is not recommended for genetic diagnostics purposes. However, thousands of kidney cells, washed out from the kidney tubules can be found in our urine. In this work, we isolated and cultured kidney cells from the urine of a person carrying the genetic variant

in *NPHP3* and from the urine of a healthy person. Comparison of the way the *NPHP3* gene is processed in these cells revealed that indeed the variant was causing an abnormal processing in a kidney-specific manner and is therefore likely to be the cause of the disease.

In conclusion, our work shows that attention should be paid in the interpretation of synonymous variants that may affect tissue-specific gene processing. Moreover, it shows that urine can work as a liquid biopsy of the kidney, when kidney cells are isolated and cultured, and this can have important applications in the genetic diagnostics of inherited kidney disease.

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Human urine-derived renal epithelial cells provide insights into kidney-specific alternate splicing variants.
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