

Editorial

Why should genetic testing be incorporated into routine clinical practice in nephrology? The utility of specialized clinics. An emerging need

¿Por qué se debe incorporar el estudio genético a la práctica clínica habitual en nefrología? La utilidad de consultas monográficas. Una necesidad emergente

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Introduction

"The lineage of such men as you cannot have been lost."

Menelaus, *The Odyssey*

"An exact determination of the laws of heredity will probably work more change in a man's outlook on the world and in his power over nature than any other advance in natural knowledge that can be clearly foreseen."

William Bateson, 1900

Chronic kidney disease (CKD) is a worldwide public health problem. Approximately 1% of the population requires renal replacement therapy, but it consumes up to 5% of the health system budget. The assessment of the prevalence of CKD and the development of specific programs in health systems to reduce its consequences are currently considered basic public health strategies.^{1,2} According to the latest records of the Spanish Society of Nephrology, the incidence of CKD in Spain is 151.9 pmp, with a wide range from 41 pmp in those younger than 44 years to 474.1 pmp in those older than 75 years, depending on the age of the population studied.³

One of the main problems when dealing with CKD in public health programs is the high percentage of patients who are diagnosed in very advanced stages of the disease, a circumstance that undermines the effectiveness of preventive programs. At present, the mechanisms responsible for kidney disease remain unknown, and few therapies are directed at a specific target. Approximately 25% of patients with CKD have or present a family history and Mendelian causes represent about 10% of the etiologies of CKD, and are the main cause of nephropathy in children.⁴⁻⁷

It is estimated that approximately 10% of adults worldwide with a recent diagnosis of CKD have an "unknown," "other," or "not affiliated" cause of disease. This lack of specific or, at best, ambiguous diagnosis prevents adequate clinical management, which makes it impossible to use targeted therapeutic approaches. In Spain, the results are no more flattering, with a high percentage of patients lacking precise diagnoses, as reflected in the records of the Spanish Society of Nephrology for the following age groups the "unknown diagnosis" is: 15–44 years, 7.2%; 45–64 years, 25.6%; 65–74 years, 27.9%; and >75 years, 39.3%.⁸

There are few studies on the cost-effectiveness of genetic analysis for the early and reliable diagnosis of renal diseases and family diagnoses.^{9,10} Many patients are diagnosed at advanced stages of CKD (stages 4 and 5), at which time renal biopsies do not usually provide valid information, hence the interest in early diagnosis. Complete exome sequencing (part

DOI of original article:

<https://doi.org/10.1016/j.nefro.2022.02.005>.

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of the genome formed by the exons, i.e., the coding parts of the genes that will be part of the ribonucleic acid-messenger RNA) is emerging as the first-line diagnostic method in some disciplines. However, its utility had not been adequately examined in renal diseases until the recent appearance of two papers that analyzed it in both adult and pediatric populations. The first of these studies, carried out in the adult population at Columbia University in New York, studied 3,315 patients with CKD, identifying genetic alterations in 307 of them (9.3%), in accordance with the diagnostic variants defined and classified as pathogenic or probably pathogenic according to the guidelines of the *American College of Medical Genetics and Genomics*.¹¹ Sixty-seven percent of the diagnosed entities had autosomal dominant inheritance, 14% autosomal recessive and 18% X-linked inheritance. The main etiological diagnosis was related to renal cystic diseases, followed by collagen mutations and glomerular diseases. The percentage of patients in whom a genetic alteration was identified was very similar to that of oncology patients, in whom genomic diagnosis is routinely employed. One of the most important messages of this study is the importance of the clinical implications on the progression of nephropathy, family information and counseling, the utility in selecting a family member as a potential living donor, and the systemic implications of an etiological diagnosis. Thus, the genomic diagnosis of these patients caused 53% of the patients to be referred to and evaluated by other specialists for presenting or associating with other extrarenal clinical manifestations. The genetic diagnosis meant that in 89% of the cases the clinical management of the patients was modified, either with the suspension or initiation of immunosuppressive treatments, or through the option of including the patients in clinical trials, and above all with the possibility of carrying out targeted therapies, avoiding unnecessary invasive procedures. In light of these studies, it will probably be necessary to reconsider the classification of diseases based on a molecular classification. Sequentially, Mann et al. have published their results of complete sequencing of 104 pediatric patients at the time of kidney transplantation at *Boston Children's Hospital* in 2007–2017.¹² Exome studies in patients under 25 years of age with CKD have identified pathogenic mutations related to their kidney disease in 20% of them.¹³ In this group of 104 patients, pathogenic genomic alterations were identified in 34 patients (32.7%), which translated into important implications in their management and clinical approach. The diagnosis of diseases such as primary hyperoxaluria type I, Fabry disease, Dent disease or the presence of mutations in glomerular diseases entails very important changes in treatment, prognosis, and family information. For all these reasons, there are more and more voices in the scientific world that advocate a genetic approach in patients with renal disease of unknown origin. Supported by its proven clinical utility in different scenarios and the progressive reduction in price, the exome study is becoming an efficient and cost-effective diagnostic test.

Considering the recent data published in the medical literature and the high percentage of patients in Spain with CKD of non-inherited etiology, we believe that genetics should be progressively incorporated into routine clinical practice. In this editorial we will outline some of the preliminary data following the development of a specialized clinic on possible

hereditary diseases attached to the Nephrology Department of the Hospital Universitario 12 de Octubre. The development of this consultation should provide answers to a series of questions such as: how to incorporate genetic diagnosis into a nephrology consultation in the public health system?, should it be incorporated?; is it cost-effective?; is it clinically profitable?; does it have ethical implications?

A walk through history

"This missing science of heredity, this unworked mine of knowledge on the borderland of biology and anthropology, which for all practical purposes is as unworked now as it was in the days of Plato, is, in simple truth, ten times more important to humanity than all the chemistry and physics, all the technical and industrial science that ever has been or ever will be discovered."

Herbert G. Wells, 1903

The history of genetics has its origins in the gloomy garden of a Moravian monastery, where the botanist and monk Gregor Mendel grew his peas and in 1864 ended up creating the term "gene," which would fall into disuse a few decades. This story intersects with Darwin's theory of evolution and both circumstances fascinated English-speaking reformers. The great wars that ravaged Europe caused the gene theories to be forgotten, theories that were taken up again after World War I by Nazi Germany, with its theories on eugenics. After World War II, a chain of discoveries set in motion a revolution in biology with the identification of deoxyribonucleic acid (DNA) as the source of genetic information. In 1971, genetics underwent one of its greatest transformations with the creation of the first recombinant DNA molecule by Berg and Jackson. Previously, James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin had discovered the three-dimensional structure of DNA and disseminated the iconic image of the double helix. The 1970s would be marked by technologies that transformed genetics, such as gene sequencing and cloning. In the 1980s, geneticists began to use these techniques to map disease-related genes. Walter Gilbert, one of the pioneers of DNA sequencing, had written on the edge of a napkin an estimate of the cost and manpower required to sequence all three billion base pairs of human DNA. According to Gilbert, some 50,000 people would have to be employed for a year, and his work would cost about \$3 billion, one dollar per base. The Human Genome Project was launched on January 29, 1983. In 1993, the gene for Huntington's disease was isolated, followed by the gene for cystic fibrosis. The identification of disease-related genes heralded a new era of genetic intervention and was the prologue to the history that biologists are now writing.

At the beginning of the 1990s the main gene related to polycystic kidney disease, the PKD1 gene, located on chromosome 16, was identified, and later D. J. Peters, of the University of Leiden, identified the second gene involved in the development of this disease, the PKD2 gene, located on chromosome 4.¹⁴⁻¹⁶ These discoveries have made it possible to establish a close genotype-phenotype correlation over the years. At present, it is likely that there are more than 100 hereditary nephropathies, a number that is increasing every day thanks to massive exome sequencing techniques. In 2016, researchers

described the third gene related to polycystic kidney disease, the GANAB gene, and at the end of 2018, others discovered a fourth gene with possible pathogenic involvement, named DNAJB11.^{17,18} Finally, in late 2019, researchers reported a fifth gene, ALG9, with pathogenic implications for the development of renal and hepatic cysts.¹⁹

In short, this leisurely stroll through history will become a frenetic journey in the years to come, punctuated by constant genetic discoveries and numerous attempts to establish clinical correlations, targeted treatments and gene therapies that will change the natural history of medicine. From that quiet monastery in Moravia to a myriad of virtual networks that will probably surpass all the expectations dreamed of by the brilliant researchers who devoted their lives to scrutinizing the mysteries of a double helix that allowed them to move into reveries that will probably come true in the coming decades. The solitary wanderer, Mendel, probably harbored dreams, that Jean-Jacques Rousseau could not have imagined in the 18th century, when he wrote his erudite words as a testament.

Justification

The high percentage of patients with CKD of non-familial etiology has deleterious consequences on therapy, does not allow predicting the possibility of recurrence of the primary disease after receiving a renal transplant, and prevents family counseling and studies from being performed in the rest of the potentially diseased family members. In turn, it may lead to unnecessary invasive interventions, such as sterile immunosuppressive treatments or, on the contrary, the exclusion of patients who could benefit from them.

The creation of a specialized clinic for hereditary diseases leads to a more rational use of resources and not necessarily to an increase in costs, as initially might be expected. The correct diagnosis of hereditary diseases correlates with a better therapeutic approach and with the recognition of all familial cases, making it possible to adopt preventive follow-up measures, which can translate into marked economic savings, a reduction in complications and a clear decrease in the development of CKD. The development of CKD involves, as is well known, an enormous economic cost for the system and a great emotional burden for the families, who are reflected in the evolutionary mirror of their predecessors.

For all these reasons, the incorporation of genetics in selected cases of patients with CKD of unknown etiology has important implications for the health system and, therefore, the creation of a hereditary disease clinic can be considered a preeminent necessity in current nephrology.

Objectives

The main objective of these clinics should be to establish a reliable diagnosis in those patients with CKD of unknown etiology or to confirm clinical suspicion in those patients with a high suspicion of genetic renal disease.

Among the secondary objectives, we highlight the following:

- Incorporate the Genetics Service into routine clinical practice, not only through the performance of diagnostic genetic studies, but also through its fundamental role in genetic counseling.
- As a result of the above, it is essential to establish preimplantation embryo selection programs in women of childbearing age.
- Avoid unnecessary and ineffective diagnostic tests and intensive treatments. Adapt the patient's treatment to his or her needs.
- Optimize the complementary tests requested, avoiding unnecessary and lengthy explorations in the absence of a diagnosis of certainty.
- Incorporate patients into clinical trials aimed at the specific therapeutic target.
- Incorporate other hospital services, given that in many cases these are systemic diseases that require the collaboration of other specialists.
- Enable training of nephrologists and even other specialists interested in hereditary renal diseases.

Preliminary experience

Following this line of thought, in March 2017 the Nephrology Service of the Hospital Universitario 12 de Octubre de Madrid decided to create a specialized clinic for cystic and hereditary renal diseases. The service generated a protocol for the early identification of these diseases, with all patients previously diagnosed in other nephrology outpatient clinics referred to this clinic. In addition, we discussed this protocol with the hemodialysis units in our health area, as well as with the renal transplant clinic in an attempt to identify descendants of the affected patient (*index case*) who were potential carriers of the disease. At the same time, an information sheet has been prepared for the 18 primary care centers dependent on our hospital for the early identification of patients with cystic kidney disease or hereditary kidney disease.

Since December 2013, the Hospital Universitario 12 de Octubre has served an area of approximately 400,384 inhabitants. Taking into account the incidence and prevalence of CKD in Spain and in the Community of Madrid, as well as the percentages of non-inherited CKD in Spain by age group, it was estimated that in one year we could evaluate approximately 200 patients with potential inherited diseases.

The support of the Genetic Service of our hospital is fundamental in this collaboration. They perform an additional evaluation, generating a genealogical tree for every patient who is going to undergo a specific genetic study due to suspicion of hereditary renal disease. This allows a proper study of the patient and its family with the possibility of identifying a larger number of affected patients. Since June 2019, the possibility of performing a complete exome sequencing has been incorporated. This makes it possible to considerably enrich and increase the cost-effectiveness of genetic studies.

During the analysis period from March 2017 to May 2019, we evaluated 280 patients with suspected hereditary disease. Patients arrived from other general nephrology (80%), pediatric nephrology (10%), other specialties (5.1%), and primary care (4.8%) practices.

As of the evaluation date, targeted genetic studies had been performed in 86 patients (31%). The mean time between requesting the genetic study and obtaining it was 2 months. The results of the studies are presented below:

- PKD1 mutation: 42 (48.8%) patients, 3 of them truncated.
- PKD2 mutation: 10 patients.
- COL4A3 mutation: 3 patients.
- COL4A5 mutation: 6 patients.
- Mutation in UMOD: 2 patients.
- NPHS2 mutation: 2 patients.
- TRCP-6 mutation: one patient.
- Other genes: 6 patients.
- Without mutations: 14 (16.3%) patients.

Some 25.7% of the patients evaluated in the clinic had mutations and in 83.7% of the patients in whom a genetic study was requested, results comparable to those described in the medical literature, despite the fact that complete exome sequencing techniques were not used initially. The finding of these genetic mutations resulted in changes in the clinical and therapeutic management of the patient, as well as in important vital and prognostic implications for patients and their families. As described in the previously mentioned studies, the genetic results led to a modification in the therapeutic approach in 80% of the patients and multidisciplinary collaboration in at least 40–50 % of the cases.

Potential benefits, barriers to development and final considerations

As we have tried to reflect throughout this text, monogenic diseases are underestimated and continue to be a very important cause of CKD. It is considered that they may account for 70% of the causes of terminal CKD in children and 10–15 % in the adult population. According to data from the *European Renal Association*, 27% of patients with kidney disease have an uncertain diagnosis, and according to the *US Renal Data System*, these percentages are 22% in the pediatric population and 18% in adults.^{20,21} As reflected in a recent review by Torra et al., we should probably add the inconsistent diagnoses of hypertensive nephropathy/nephroangiosclerosis, chronic glomerulonephritis and diabetic nephropathy without renal biopsy. Regarding the latter disease, I would like to highlight the attempt by Garcia et al. to find a risk score, pending definitive validation, to predict which patients with diabetes mellitus should undergo a potential renal biopsy for presenting a high probability of suffering a nosological entity other than diabetic nephropathy.²² In addition, about 30% of patients with CKD have a family member with the disease, which points to the genetic substrate of many of these conditions.

Mutations in about 400 genes have been linked to inherited renal diseases. Early detection of these mutations may have important implications for the patient and family, in terms of treatment, prognosis, genetic counseling and screening in at-risk relatives. The use of next generation sequencing techniques has significantly increased the diagnostic possibilities.

The percentages of certainty of diagnosis have increased to 55–80 % in patients with Alport syndrome and up to 64% in patients with suspected tubulopathies.^{23–25} Therefore, there is a widespread consensus on the benefits of its use in routine clinical practice. Among them, we could highlight the following:

- The possibility of reaching an accurate diagnosis of the underlying cause of the disease by a minimally invasive and increasingly cost-effective method. It can avoid the "odyssey" of unnecessary and invasive diagnostic tests (e.g., renal biopsy) that can lead to misdiagnosis and incorrect and deleterious treatment. One of the most illustrative examples is that of Alport syndrome, an entity that is often mistaken for primary focal segmental hyalinosis, with the consequent use of immunosuppressive treatment.
- It enables the search for and potential treatment of specific extrarenal manifestations, with the need for the participation of other specialties.
- It provides guidance for making *appropriate* therapeutic decisions (e.g., avoiding immunosuppressive treatments in genetic forms of nephrotic syndrome) and establishes a more accurate prognosis.
- It can be crucial to perform appropriate genetic counseling ranging from recurrence, through risks and ending with reproductive options (*preimplantation embryo selection*), and in some cases, pre-symptomatic studies.
- Its impact on renal transplantation, especially in living related donor renal transplantation.
- It can lead to significant economic savings, although cost-effectiveness studies are necessary.

Despite the strong evidence supporting its utility, its use continues to be scarce in clinical routine, especially in adult nephrology. Among the main limitations to its implementation, the following should be highlighted:

- Concern about its costs and generalization in the development of conventional clinical practice.
- Lack of genetic knowledge on the part of nephrologists.
- Need for multidisciplinary teams.
- Lack of perceived benefit.
- Difficulty in interpreting genetic variants.
- Need for pre- and post-test counseling.
- Presence of unexpected or unknown phenotypes such as allelic heterogeneity, incomplete penetrance, epigenetic regulation, mosaicism.

In Spain, great advances have been made in recent years to try to increase the percentage of patients with a reliable diagnosis. We would like to highlight the work of R. Torra's group, whose work, extensive experience, and good teaching have brought genetics closer to the routine practice of nephrology. His recent publication on Alport syndrome with autosomal dominant inheritance is, once again, a relevant contribution that may lead to a paradigm shift in the approach to these patients.²⁶ In line with this group, many nephrology departments have joined this attempt to incorporate genetics into the conventional practice of nephrology.

In short, the ultimate goal is to make the complex seem easy, so that its use becomes a routine practice, always under the protection of a judicious use.

In line with the possible upcoming changes in the use of genetics in the medicine of the future, we would finally like to highlight a recently published experience on the ultrafast use of genome sequencing. This work describes, for the first time, a method of ultrafast genome sequencing in critically ill patients. It was developed in 12 patients from two centers at Stanford; in five of them an early genetic diagnosis is established with a time to result of less than 8 h. The authors conclude that these techniques can guide the clinical approach, improve prognosis, and reduce costs in these types of patients.²⁷

Epilogue

Rita Levi-Montalcini received the Nobel Prize in Medicine in 1986 for her discoveries on growth factors in neurobiology. She thus became one of only 12 women to have received the Nobel Prize in Medicine and Physiology, taking over from Gerty Theresa Cory, the first woman to receive the prize in this category for her discoveries on the catalytic conversion processes of glycogen. In one of her delightful books, which doubles as a memoir, entitled *In Praise of Imperfection*, the Turin-born Rita Levi-Montalcini perfectly expresses the following words: "Truth is not a fact that we can discover, just as we cannot know in advance which observations are relevant and which are not; every discovery, everything that helps us to understand better, is born as a prediction of what can be. This predictive imagination is a creative act of the mind; it is mental work, an inner inspiration, not the consequence of a programmed investigation."

This editorial was born from a similar inner inspiration, I believe, and from the need to incorporate genetics into the new medicine. G.C. Lichtenberg, an 18th century German scientist and writer, said that there is no more interesting surface on earth than the human face, and I dare to say that in medicine there is no more interesting surface than the set of genes under study.

This editorial is also born out of a fascination: a fascination with the idea that the genetic character of a disease can be revealed by clinical and, especially, phenotypic signs. That is, by what we might call the "Dorian Gray effect." The most significant thing in Wilde's story is not the unfolding of Dorian in the portrait, but the fact that the growing dissipation and abjection in the life of the beautiful young man are gradually reflected in his true face, the portrait's, which gradually becomes monstrous. In the end, the interior and exterior merge, and the latter becomes the perfect reflection of the former.

Whether it is part of the body or part of the soul, or both indistinguishable, the genome has not yet revealed its secret. On the one hand, it is the space where the inside and the outside touch and merge; a canvas on which one writes from the inside, one writes from the outside, one writes from before writing, and one does not stop writing until the end: until there is only an *outside* without an *inside*. So we live incarnated in genes that cannot stop for a moment from expressing and sig-

nifying themselves, nor from responding, for better or worse, to the challenges in their nature.

Scientists divide but clinicians discriminate. To sum the parts, we must begin by dividing the sum into parts. Once we perceive human organisms as the fruit of interactions between genes, external environments, and gene environments, our view of human beings undergoes a fundamental change. At times one comes to wonder what is normal or natural, what is not subject to variations, mutations, changes, to inconstancy. Since DNA, a molecule full of contradictions, is responsible for our code, it is not surprising that we are a set of contradictions. We look for consistency in heredity and find the opposite: variation. Mutations are necessary to maintain our individuality, they are paired opposing strands.

Genetics modifies our lives. The hope of being able to change the course of history has always been a desire. Ameliorating the consequences of adverse genetics will probably be the common thread of this project.

" Human beings are ultimately nothing but carriers—passageways—for genes. They ride us into the ground like racehorses from generation to generation. Genes don't think about what constitutes good or evil. They don't care whether we are happy or unhappy. We're just means to an end for them. The only thing they think about is what is most efficient for them."

Haruki Murakami, 1Q84

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