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Gene Suppression in Chronic Kidney Diseases

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Introduction

A significant and growing worldwide health issue is chronic renal disease. According to predictions, CKD will rank as the sixth most common cause of mortality by 2040. The ageing of the population is a contributing factor to the rising burden of CKD (CKD is 8 times more prevalent in those over 70 than in those under 40). The growing frequency of CKD is largely caused by diabetes and hypertension, which are frequent risk factors for kidney injury. With a higher incidence and greater prevalence in women, there is a clear gender disparity in CKD. Nevertheless, men are more likely to acquire ESRD than women, and women have a lower risk of CKD development. A complicated heterogeneous illness, chronic kidney disease is influenced by both genomic and environmental variables. According to estimates, CKD heritability is substantial (30–75%). Well-known clinical indicators like SCr levels, eGFR, albuminuria, or UACR can be used to detect CKD. Unfortunately, the ability of these clinical indicators to forecast individual CKD risk or likelihood of eventual development to ESRD is severely constrained. Although significant attempts have been made to comprehend the heredity of CKD, our understanding of the causative pathways is still lacking. In order to find the missing heritability, four main strategies have been put forth: investigating rare variants, enlarging sample sizes, researching molecular components unrelated to DNA sequence variations, and assessing if family studies overstated the risk of heredity. By combining data summaries from various individual GWAS, meta-analyses of GWAS have offered a useful and relatively inexpensive strategy to increase the statistical power in CKD.

Description

This has helped to mitigate the problem of small sample size and identify numerous genetic loci associated with CKD and/or kidney function traits. Also linked to CKD, eGFR, or SCr are uncommon mutations in UMOD, SHROOM3, solute transporters, and E3 ubiquitin ligases. However, because not all CKD susceptibility is explained by these genetic markers, additional factors must be involved in the remaining heritability. Instead of missing variations, some of the missing heritability may be explained by genetic interactions (epistasis).

A biological component called telomere length has been linked in a few studies to the prevalence and/or progression of CKD. The lack of coverage of structural variations in commercial arrays, including CNVs, insertions, deletions, inversions, and translocations, may contribute to the missing heritability. Nuclear genes that encode mitochondrial proteins as well as particular mtDNA-encoded genes have also been linked to CKD. The sex chromosomes, which are frequently left out of GWAS studies, may aid in explaining gender disparities in CKD. Specialized nucleoprotein complexes called telomeres aid in safeguarding the ends of linear chromosomes. The length of telomeres varies across individuals and within individuals. Increased chronological age, early life stressors, multi-system disorders, and all-cause mortality have all been linked to shorter telomere length. The majority of research has focused on the relative telomere length of peripheral blood leukocytes, however telomere length varies among tissues within a single person, with older adults showing more telomere length heterogeneity. Although the heritability of telomere length has been estimated to be between 28 and 82%, not all genetic or environmental impacts on telomere length are understood. However, this is difficult because different wet-lab techniques (such as time at sample collection, storage and processing of biological material, absolute compared to relative telomere length evaluation, platform used) and in silico analyses (such as normalisation, controls, covariates, association, and correction tools) have significant effects on the reported measurands. Meta-analysis of telomere length may help confirm discovery associations across multiple collections. Traditional epidemiological research examining the mechanism or causality of observed relationships is likewise lacking.

Genome Variation of CKD

The uremic state, together with chronic inflammation linked to increased generation of reactive oxygen species, may contribute to impaired DNA damage repair and increased chromosomal damage in CKD patients. Reactive oxygen and nitrogen species, or RONS, combined cause DNA strand breaks, point mutations, and abnormal DNA cross-linking, which result in genomic instability even if their deleterious effects on CKD have not been conclusively proven. Increased levels of C-reactive protein (CRP), a marker of inflammation, are found in CKD patients. Oxidative stress is another trait that CKD patients typically display. Gene variations that control these several pathways may have an impact on the development and/or incidence of CKD. Recent genome-wide association studies (GWASs) on sizable European populations have revealed novel genetic risk single-nucleotide polymorphisms (SNPs) linked to a variety of CKD-related pathologies, including hypertension, coronary artery disease, subclinical vascular disease, and functional kidney traits in CKD patients. Other investigations have revealed a connection between the genetic variations underlying cardiovascular diseases and kidney characteristics. Beyond the most often studied tumors, there is evidence that telomere length is connected to disease states, notably age-related disorders. Premature telomere shortening is related to the number of months to years spent receiving dialysis treatment.

Despite women having a higher average age in this cohort, a cross-sectional research of 175 hemodialysis patients found that men with CKD had shorter telomere length; a link between shorter telomeres and getting older and being male was also noted. Comparing 203 age- and sex-matched controls without CKD to 203 Japanese hemodialysis patients, shorter telomeres were related with CKD, and shorter telomeres were also associated with new onset cardiovascular events. In the general population, a less reactive immune system is linked to healthy ageing, and ESRD accelerates premature immunological ageing, with shorter telomeres seen in 137 patients with ESRD compared to 144 people without renal disease. Age-related decreased telomere length was demonstrated in histologically normal and diseased human kidney tissue samples from 24 individuals. Telomere length is generally shorter in the cortex than in the medulla. An essential aspect of renal fibrosis is premature senescence, which is accelerated by stressful conditions like increased ROS and higher glucose levels. Numerous animal models of kidney disease demonstrate that telomere shortening is associated with renal failure; however, precise telomere measurement necessitates a rigorous experimental design. Shorter telomeres may also hinder recovery from acute kidney injury, according to research on renal ischemia/reperfusion injury in wild-type and telomerase deficient mice. In a rat model of chronic rejection, severe renal

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failure causes telomere shortening, with fast telomere loss shown during kidney transplantation.

The true relationship between telomere length and CKD will be determined by large-scale investigations using meticulously obtained biological samples with standardised phenotypes and analysis techniques. Although there are potential treatments to reduce premature telomere shortening, further research is required to determine the mechanistic relationships between telomere length and kidney function. Copy number variations are structural genetic changes that result in the deletion or duplication of DNA regions. This can happen across the entire genome and affect DNA regions that are kilo- to mega-base pair long. It can also lead to aberrant gene amplification. CNVs are an important source of genetic variation associated with both population variety and disease, including cancer, neuropsychiatric disorders, and renal diseases. CNVs can be inherited or develop spontaneously. There is frequently ambiguity regarding the genetic causes of CKD in juvenile patients, however current research suggests that chromosomal microarrays may help to partially resolve this. The adoption of next-generation sequencing (NGS) in clinical practise has been made possible by improvements in NGS techniques, such as whole exome sequencing, which have made it possible to sequence huge portions of the genome at a reasonable cost. Chronic kidney disease (CKD) raises the risk of morbidity and mortality and contributes significantly to the global burden of disease. A wide range of basic renal diseases can lead to CKD. One in five people with CKD cannot be diagnosed with a primary renal disease. Furthermore, current research suggests that a significant portion of patients may have the clinical diagnosis wrong. An inaccurate diagnosis or a lack of a diagnosis may have therapeutic repercussions. In CKD patients, particularly those with an unclear cause, genetic testing may improve diagnosis accuracy. While recent studies indicate that genetic testing can also be a useful diagnostic tool for adults with CKD, the diagnostic value of NGS has been mostly demonstrated in juvenile CKD cohorts. NGS can aid in the diagnostic process in kidney illnesses with an atypical presentation, where it may result in reclassification of the primary renal disease diagnosis, in addition to its implications for unexplained CKD. Only a small number of studies have examined the diagnostic efficacy of NGS-based methods in individuals with unexplained CKD to date.

24–34% of CKD patients report a favourable family history, and familial clustering is a frequent occurrence in individuals with end-stage renal disease (ESRD). This shows that it is important to consider the potential of a genetic aetiology during the diagnostic workup of a CKD patient. This is corroborated by the fact that hereditary kidney illnesses are a prevalent cause of ESRD in both adults and children, and that monogenic mutations are frequently discovered in early-onset CKD. 17% of individuals with ESRD are classified as having CKD of unclear aetiology since they do not have a primary renal disease (PRD) diagnosis. Furthermore, the first diagnosis is frequently wrong in patients. Giving these patients the right diagnosis could have therapeutic ramifications. In the case of an atypical hemolytic uremic syndrome (aHUS) genetic mutation, the availability of certain monoclonal antibodies that target the complement system may offer vital therapeutic options. Additionally, particularly when living-related donation is involved, a genetic diagnosis may be crucial for family counselling and in the context of kidney transplantation. One in ten persons can have a molecular diagnosis determined by next-generation sequencing (NGS), according to a recent study in a group of CKD patients, 65% of whom had ESRD.

When taking into account patients with unexplained CKD or those with an atypical presentation, it is expected that the proportion of patients in whom a molecular diagnosis can be made is even larger because unexplained illnesses have a higher likelihood of having a genetic origin. However, only a small percentage of these patients are being subjected to genetic testing. In patients with CKD of uncertain origin, NGS-based approaches are thus anticipated to increase the diagnostic precision. Additionally, NGS-based testing may be able to identify the underlying cause of CKD at an early stage of the condition, allowing for prompt intervention to halt or stop the progression of ESRD. The utility of NGS-based multi-gene panels and whole exome sequencing for these patients in clinical practise, however, needs to be proven given the novelty of the approach. In circumstances where there is a higher likelihood of a hereditary form of CKD, such as patients with familial CKD, early-onset CKD, an atypical disease course, or patients with an unidentified aetiology of CKD, genetic testing can be crucial in accurately diagnosing PRD. Contrary to diagnostic renal biopsies, which frequently fail to yield a diagnosis in extremely early or late stages of the disease, genetic testing can identify the cause of disease regardless of the disease stage. Genetic testing is additionally non-invasive and can accelerate the diagnostic journey.

A genetic diagnosis can help with family planning, kidney transplantation choices, focused surveillance of extra-renal traits, treatment recommendations, and genetic counselling. Relatives of patients with hereditary CKD may potentially benefit from counselling and genetic testing. Relatives who are otherwise healthy but have a genetic risk mutation may be eligible for monitoring and early intervention to stop the advancement of CKD and its side effects, such as cardiovascular disease. Additionally, it can disqualify the relative from living kidney donation in order to lower the chance of developing CKD in the future. Advances in NGS have made it possible to sequence huge portions of the genome at a reasonable cost, which has aided diagnostic genetic testing. Massively parallel sequencing (NGS), often known as NGS, enables the simultaneous sequencing of several genes involved in a specific trait (gene panels), all 20,000 protein-coding genes (whole exome-sequencing), or the complete genome (whole genome sequencing). Each strategy has benefits and drawbacks of its own. Gene panels frequently produce a higher diagnostic yield than whole exome sequencing (WES) or whole genome sequencing (WGS) due to their increased sequencing coverage and depth [1-5].

Conclusion

However, depending on the capture devices employed, the coverage and depth of NGS-based methodologies differs. As new updates and methods, such capture free WGS, become available, the coverage and depth of a system will also alter over time. Therefore, picking a good system is crucial. Because gene panel testing is only intended to include a pre-selected sample of genes, the possibility of incidental discoveries is reduced. Gene panels have the drawbacks of needing to be updated frequently to incorporate newly discovered genes and the inherent need for a correctly interpreted clinical context in order to prevent the performance of an incorrect gene panel.

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