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Methylation of DNA is linked to Kidney Function and Damage

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Perspective

DNA methylation is a biological process that adds methyl groups to the DNA molecule. Methylation has the ability to alter the activity of a DNA segment without changing its sequence. When DNA methylation occurs in a gene promoter, it typically acts to suppress gene transcription. In mammals, DNA methylation is required for normal development and is linked to a number of key processes such as genomic imprinting, X-chromosome inactivation, transposable element repression, ageing, and carcinogenesis.

Chronic kidney disease (CKD) is a significant public health problem. It affects more than 10% of adults worldwide, and more than 40% of people aged 70 and older. CKD is a leading cause of death worldwide, contributing significantly to cardiovascular morbidity and mortality. Chronic kidney disease (CKD) is defined as the presence of abnormalities in kidney structure or function over time. The most commonly used kidney function measures are the glomerular filtration rate (eGFR), which is usually calculated from serum creatinine concentrations, and the urinary albumin-to-creatinine ratio (UACR).

Elevated UACR is a marker of kidney damage that is used to diagnose and stage CKD and is linked to diabetic and hypertensive kidney disease. Even moderately elevated UACR is associated with an increased risk of cardiovascular disease, independent of other kidney function markers such as eGFR.

CKD and eGFR familial aggregation studies revealed a significant heritable component of up to 54 percent. Classical monogenic diseases account for only a small portion of this heritability. Rather, DNA sequence variants in many genes, environmental factors, and their interactions all influence CKD susceptibility. Genome-wide association studies (GWAS) have successfully identified common variants associated with kidney function at over 400 genetic loci. The index variants at known eGFR-associated loci are estimated to explain 8.9 percent of eGFR variance.

A GWAS meta-analysis of eGFR integrated open chromatin regions with small sets of single nucleotide polymorphisms was recently published (SNPs). This study's findings support the significance of altered transcriptional regulation as a mechanism contributing to CKD. Epigenome-wide association studies (EWAS) of eGFR and CKD were conducted to investigate DNA methylation in relation to kidney function. DNA methylation has been studied at CpG sites (CpGs) with single-base resolution as a key regulator of transcription that can be assessed in a cost-effective and high-throughput manner. Previously, researchers conducted a EWAS on 4859 adults from two population-based studies and discovered 18 validated, differentially methylated sites in whole blood that are associated with eGFR. Despite the fact that this study shed light on gene regulatory mechanisms governing kidney function, the associated CpGs explained only 1.2 percent of the eGFR variance. Other previous studies either focused on CKD patients and/or diabetes patients or patients with Human Immunodeficiency Virus infection, or were limited by a small sample size, a lack of replication, a lack of adjustment for potential confounders, or a combination of these factors. Other studies concentrated on the DNA methylation patterns of patients with diabetic kidney disease (DKD).

In this study, they used a EWAS of kidney function traits to find additional CpGs associated with gene regulatory mechanisms that may be important in CKD. They expanded the previous EWAS for eGFR and CKD by significantly increasing the sample size to 33,605 people. Furthermore, as additional traits, they included UACR and moderately increased albuminuria (microalbuminuria). The EWAS were mostly conducted in population-based studies that controlled for gender, age, diabetes, hypertension, and body mass index (BMI), smoking status, and the proportions of the most abundant white blood cells. They replicated our EWAS results in different samples, linked the CpG sites to gene expression levels in different tissues, applied the findings to clinical outcomes, and investigated the relationship between DNA methylation and kidney function.

Exogenous stress, such as UV radiation and chemicals, and endogenous stress, such as reactive oxygen species, DNA replication errors, spontaneous reactions, and mechanical stress, can all cause DNA damage. Chronic stimulation by these stresses causes DNA damage, which has been linked to ageing and a variety of diseases. Eukaryotes have a DNA repair system that responds to DNA damage in order to maintain genome integrity for survival. There are several types of DNA damage, including double-strand breaks (DSBs), base adducts, interstrand crosslinks, and mismatches. Base adducts include oxidative and alkylating lesions, some of which are mutagenic or toxic, such as 7,8-dihydro-8-oxoguanine. Interstrand crosslinks are toxic DNA lesions that prevent transcription and replication by interfering with DNA strand separation. Base mismatches occur during DNA replication and recombination. Non-homologous end joining (NHEJ), homologous recombination (HR), base excision repair (BER), nucleotide excision repair (NER), trans-lesion synthesis, and other DNA repair pathways repair damaged DNA.

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