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EPIGENETICS

EWAS of kidney function

DNA methylation is a key regulator of transcription, but how changes in methylation relate to altered kidney function is not well understood. Now, Anna Köttgen and colleagues identify epigenetic signatures associated with reduced estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) in an epigenome-wide association study (EWAS) that involved whole-blood DNA methylation analysis of two population-based cohorts comprising 4,859 participants.

As the researchers previously found that common genetic variants in CKD were enriched in gene regulatory regions, they set out to study the association between DNA methylation and kidney outcomes. They first determined DNA methylation at ~450,000 CpG sites across the genome and cross-validated associations between the two cohorts. "We found 19 DNA methylation sites that were significantly and reproducibly associated with eGFR or CKD in both cohorts," says Köttgen.

Next, to investigate whether the findings in blood translated to kidney tissue, the researchers examined the CpG sites at which DNA methylation was reproducibly associated with kidney function. Five of these CpG sites showed a significant association between DNA methylation status and the degree of renal fibrosis in kidney biopsy samples. "Some of the significant sites mapped to active enhancer regions in kidney cortex samples, suggesting that gene regulation in the target organ is a mechanism influencing kidney function," adds Köttgen. Moreover, mapping of eGFR-associated CpGs showed significant enrichment for binding sites of the transcription factors CEBPB, EBF1 and EP300.

In the future, the researchers plan to include additional study populations in their analyses. "EWAS in larger cohorts will result in improved statistical power to identify additional CpG sites, to better address questions of causality and coherence between associated sites, and to gain insights regarding the role of epigenetic factors in kidney pathophysiology," comments Köttgen.

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ORIGINAL ARTICLE Chu, A. Y. *et al.* Epigenome-wide association studies identify DNA methylation associated with kidney function. *Nat. Commun.* **8**, 1286 (2017)