SIGNIFICANCE STATEMENT

This work unravels the critical role of epigenetic modification for nephron formation and nephron number. Our study shows that although de novo DNA methylation is dispensable for nephron development, lack of maintenance DNA methylation leads to severely hypoplastic kidneys in the mouse model. Using whole mount optical projection tomography and 3D reconstructions of embryonic and neonatal kidneys, we identify a dysregulation of nephron stem cell identity leading to impaired nephron differentiation. RNA sequencing highlights the transcriptional programs regulated in the nephron progenitor cell pool and links DNA methylation to the upregulation of germline genes and endogenous retroviral elements, leading to an IFN response and cell cycle inhibition.