Cardiometabolic diseases such as coronary artery disease (CAD) and type 2 diabetes (T2D) are highly prevalent, complex diseases that remain top leading causes of deaths worldwide. This talk will focus on our recent efforts in dissecting the molecular underpinnings of cardiometabolic diseases using systems genomics approaches. We tackle the molecular complexity by integrating multi-omics data from human populations and animal model systems to retrieve tissue-specific gene networks and pivotal regulators that mediate the genetic and environmental risks of CAD, T2D, and metabolic syndrome. These efforts have revealed shared molecular pathways and gene networks between diseases, as well as disease- and risk-specific genes, pathways, and networks. For instance, immune processes and the extracellular matrix emerged as potential central orchestrators of cardiometabolic diseases. These network-level insights may help guide the development of network-based medicine for CAD and T2D.