Crohn’s Disease (CD) is a chronic heterogeneous inflammatory disorder with distinct patterns of clinical behavior driven by an inappropriate innate immune response to enteric microbes in genetically susceptible hosts. To better understand the cellular and molecular mechanisms that contribute to disease and that guide this clinical heterogeneity, we have generated and analyzed gene transcription and regulation data in mouse models of chronic intestinal inflammation and in human CD patients. Through these studies, we show that the disease state is not only associated with altered transcriptional profiles, but also the underlying gene regulatory state as seen through the accessible chromatin landscape and micro RNA expression is significantly changed in complementary ways. Using these data, we uncover two distinct molecular subtypes in CD that show strong associations with clinical phenotypes.