The study of risk factors for psychosis has been approached through multiple avenues, including studies of youth at clinical high risk for the disorder and investigations of copy number variants or structural genetic mutations that confer risk. Each approach can inform and provide insight to the other, potentially resulting in synergistic models for understanding the ways in which heterogeneous genetic etiologies can affect brain development and ultimately behavior, converging in a final common pathway to this debilitating disorder. In this seminar, I will critically evaluate, from a longitudinal perspective, the extent to which genetic and neurodevelopmental factors that place youth at either clinical or genetic high risk for schizophrenia converge. Findings will be presented from multimodal neuroimaging studies of 22q11.2 deletion syndrome (22q11DS), a contiguous gene deletion disorder that conveys the greatest increase in risk for schizophrenia in the population. In addition, parallel findings from the North American Prodrome Longitudinal Study (NAPLS), which has followed ~250 youth at clinical high risk for psychosis for 2 ½ years, will be discussed. An integrative discussion will focus on commonalities found across these cohorts, in an effort to identify factors that can lead to early identification of - and mechanistically informed interventions for - individuals who are at heightened genetic or clinical risk.