Title: Where are we with the autisms?

Rapid progress is being made on a number of fronts with regard to understanding the etiologies that underlie the autisms. The autisms are among the most common of neurodevelopmental disorders, and are highly heterogeneous in disorder phenotype, longitudinal trajectory of symptoms and response to treatment. A brief overview of the current state of thinking regarding the genetic and environmental risk factors will be discussed. Work from our own laboratory will be the focus of the remainder of the lecture. The convergence of the human genetics studies in autism and basic developmental neurobiology suggests that MET signaling is important for the proper assembly of forebrain circuits, with dysregulation leading to functional disruptions in both model systems and in humans. We discovered that a single nucleotide polymorphism in the 5’ regulatory region of the human MET gene is strongly associated with autism. This variant is functional, as it reduces gene transcription by interfering with SP1 transcription factor binding. Moreover, studies of human postmortem samples show that MET and other upstream molecules that regulate MET signaling are dysregulated in autism. Clues regarding the role of MET in the underlying pathophysiology of autism come from basic neurodevelopmental studies implicating MET in the differentiation of intrinsic and projecting cortical circuitry. A model of autism etiology will be presented in light of these basic and clinical research findings.