Congenital Neutropenia Syndromes – from Pathogenesis to Leukemic Transformation

Julia T. Warren, MD, PhD
University of Pennsylvania / Children's Hospital of Philadelphia

Severe congenital neutropenia (SCN) is a rare bone marrow failure syndrome characterized by severe chronic neutropenia, an arrest of granulocytic differentiation at the promyelocyte or myelocyte stage, and a marked propensity to develop acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). It has an estimated prevalence of 5 cases per million individuals. Patients with SCN are susceptible to recurrent, life-threatening infections as well as to the development of myeloid malignancy. The most common genetic variants associated with SCN are those occurring in *ELANE*, which encodes the neutrophil elastase**.** *ELANE* mutations also are found in the majority of cases of cyclic neutropenia, a related disorder of granulopoiesis characterized by recurrent episodes of neutropenia with a 14-35 day periodicity. Although several other genes have been identified as causes of SCN, the genetic cause of approximately 30% of SCN cases remains unknown. The identification of novel genes causing SCN and the elucidation of their molecular pathogenesis has already allowed for the development of targeted therapies and holds promise for future therapeutic interventions. In this presentation, we will review both well-established and recently identified genetic causes of congenital neutropenia. We will emphasize the divergent mechanisms underlying impaired granulocyte formation, and discuss the fascinating observation that despite this, many forms of SCN appear to share common somatic genetic events on pathway towards malignant transformation. Finally, we will compare proposed mechanisms of MDS/AML development observed in most SCN disorders to the congenital neutropenia disorder Shwachman-Diamond Syndrome. We will end with a brief discussion of how understanding these events can lead to improved monitoring and help answer major emerging questions in the field.