Project Title:

Inherited bone marrow failure syndromes: from genomic discoveries to biology

Project Description:

Inherited bone marrow failure syndromes (IBMFSs) comprise over 20 rare genetic diseases; e.g. Fanconi anemia and severe congenital neutropenia. The blood producing organ (bone marrow) in the patients does not work from early childhood, leading to low blood counts. Patients suffer from infections, fatigue and bleeding, which often require life-long transfusions or bone marrow transplantation, and also have a high risk of cancer. Since the medical needs and response to treatment vary among the diseases, accurate diagnosis is crucial. We found that many patients with inherited types of bone marrow failure have new diseases that had not been previously defined. These new IBMFSs are likely caused by mutations in new bone marrow failure genes. In 2001 we established a nationwide registry of IBMFSs (database and sample repository) with more than 300 patients. We propose to identify new genes for bone marrow failure by using a new technology (called exome sequencing) and characterize a subgroup of 42 patients who are suspected to have new diseases. Then, we propose to study one new IBMFS with a new bone marrow failure gene that we successfully discovered using the above approach, to understand how the disease ensues. Specifically, we will focus on a breakthrough discovery from our lab that a perturbation of chemical machinery in the cells, called RNA degradation, causes a human disease with severe bone marrow failure. We will study how mutations in the new bone marrow failure gene change the delicate balance of gene products (RNA) and impair blood cell formation in two complementary disease models: patient blood cells and zebrafish blood cells. The results of our study will have a major impact on the care of patients with IBMFSs by providing new genetic tests to establish diagnoses, counsel the families, and tailor treatment and cancer surveillance plans. Our findings will help understand how marrow failure develops, and prompt research for new therapies.