

**Department of Immunology**

**Seminar** Tuesday January 10, 2012, 16:00 hr, library 8<sup>th</sup> floor (Ee-822)

**"Deleterious LRBA mutations in a novel syndrome of immune deficiency and autoimmunity"**

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Genetic causes of childhood-onset hypogammaglobulinemia are currently unknown. Most patients are sporadic, but autosomal dominant (AD) and autosomal recessive (AR) inheritance have both been described. We performed genetic linkage analysis in consanguineous families with hypogammaglobulinemia. Four consanguineous families with childhood-onset humoral immune deficiency and features of autoimmunity shared genotype evidence for a linkage interval on chromosome 4q. Sequencing of positional candidate genes revealed that patients in each family carried a distinct homozygous mutation in LRBA (lipopolysaccharide responsive beige-like anchor protein). Functional analyses indicated that LRBA has a role in B and T cell survival, as cells showed reduced proliferation, increased apoptosis and phosphorylation of the pro-apoptotic molecule BAD was reduced. Interestingly, autophagy was deficient in B cells. Moreover, activation of B and T cell was impaired, as immunoglobulin production and expression of co-stimulatory molecules in T cells were reduced. We describe a novel syndrome characterized by early-onset hypogammaglobulinemia, autoimmune complications, and inflammatory bowel disease which is caused by deleterious mutations in LRBA.