Primary immunodeficiency disorders: From bedside to genomic sequencing

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SUMMARY

This thesis focuses on clinical and immunological phenotypes, and molecular pathology of selected primary immunodeficiency disorders. In particular, patients and families suffering from X-linked lymphoproliferative disease, X-linked hyper-immunoglobulin M syndrome (CD40L deficiency), and Shwachman-Diamond syndrome will be presented. Special emphasis will be given to genomic sequencing in the prenatal and postnatal diagnosis and follow-up of immunodeficient children in clinical practice. The most important findings of these studies are as follows:

- A new disease-causing missense mutation (c.47G>A) in *SH2D1A* resulting in p.G16D replacement in the amino acid sequence of the SAP protein, was discovered.
- The p.G16D protein is not able to bind to physiological ligands like SLAM and 2B4. It is proposed that he defect in ligand binding may contribute to the loss of function of the SAP protein in patients carrying p.G16D mutation.
- In a patient with severe CD40L deficiency a c.216C>A sequence variant was found that resulted in stop codon of CD40L synthesis in amino acid position 72 (p.C72X).
- Association of X-HIGM syndrome with invasive *C. laurentii* infection is first reported here.
- The first patient with severe SDS phenotype and two previously unknown *SBDS* mutations occurring in exon 3 (c.362A>C, p.N121T) and in exon 4 (c.523C>T, p.R175W) is presented.