Title: Identification and characterization of novel variants and genes involved in Primary Immunodeficiencies

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Primary Immunodeficiencies (PIDs) represent a heterogeneous group of monogenic disorders characterized by immune dysregulation, altered immune responses of innate and/or adaptive immunity and infections. More than 260 disorders have been identified, resulting from mutations in over 300 genes. Among those, combined immunodeficiencies (CID) are defined by impaired T and B cell immunity leading to increased susceptibility to infections, disorders of immune regulation and malignancies. We are interested in patients with CID and other complex phenotype [i.e. Common Variable Immunodeficiencies, CVID], to understand the genetic basis of the disease in relation to the clinical and immunological phenotype, with the ultimate goal to define the natural history and treatment of choice. Next generation sequencing (NGS) technology has opened great perspectives for the characterization of genes involved in PIDs but in several patients the causative gene has not been identified yet. We have set up and validated in collaboration with the OSR Centre for Genomics different approaches of NGS analysis, including Targeted exome sequencing, Whole exome sequencing and Whole genome sequencing to discover new genes causing inborn errors of immunity. We selected CID cases sharing lymphopenia, recurrent infections and various clinical manifestations and identified five known genes by NGS assays (RAG1; IL7-receptor; PI3KCD; MAGT1 and a peculiar inversion in WAS). Additional candidate genes, including novel genes, are under molecular and functional investigation in other patients. The PhD candidate will identify novel variants and novel genes potentially causative in the pathogenesis of the disease first by bioinformatic tools and then explore the causal link by: 1) molecular validation on DNA and RNA; 2) phenotypical (flow cytometry, Western blot) and functional studies (ie. cell proliferation, apoptosis, activation, migration) on patients’ cells aimed at the demonstration that the given variant is causing biological alterations 3) gene transfer with LV-vectors to restore the defect in patients’ cells transducing primary lymphoid cells, cell lines, hematopoietic stem/progenitor cells, fibroblasts; 4) gene editing by CRISPR/Cas9 technology to unravel the effect of the mutation in cell lines from healthy subjects and patients’ cells. Animal models will be also used to validate the involvement of novel identified genes in the immune system to recapitulate the human phenotype, with the aim of gene correction. These studies will pave the way for a depth understanding of a given immunodeficiency, thus contributing to improve diagnosis, quality of life and clinical outcome of PID and set the basis for patient-specific therapeutic strategies for those patients with unmet medical need.

Key References:


