Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary antibody deficiency, characterized by a marked clinical, immunological, and genetic heterogeneity. The degree of disease severity and immune deficiency in pediatric CVID patients may also considerably vary and apart from an increased susceptibility to infections, CVID is defined by disturbed immune homeostasis and hence, non-infectious complications, such as autoimmune, allergic, autoinflammatory disease, and lymphoproliferation also belong to its clinical features. Therefore, an antibody deficiency in CVID is a common denominator of numerous variable clinical forms and reflects the complexity of its genotype-immune phenotype correlations. Genetic studies in children with CVID will contribute to a better understanding of the immunopathogenesis of this group of PID disorders. Identifying a causative mutation will delineate the role of monogenic inheritance and also will enable us to define correlations between the genotype and clinical and immunological disease phenotype. The prognostic value of genetic studies in children with antibody deficiencies to exclude an early childhood immaturity of the immune response must be highlighted as well. Molecular diagnosis could contribute to anticipating a clinical prognosis and facilitating therapeutic decisions, and in the long-term perspective, also to elaborating innovative individualized methods of therapeutic interventions, based on achievements of precision medicine and gene therapy.

One hundred children, aged from four to eighteen years, diagnosed and treated because of immunodeficiencies with predominantly antibody production defects, are going to be enrolled in the study. Clinical characteristics and molecular investigations will be performed according to the ethical standards of the 1964 Helsinki Declaration and its later amendments, following the acceptance of the local University Bioethical Committee. In all the children studied, a precise evaluation of the clinical condition with immunodiagnostics be performed, with special emphasis on infections, autoimmune and inflammatory diseases, symptoms of immune dysregulation, and organ-specific immunopathology.

The molecular genetic analysis will be targeted on uncovering the background of monogenic CVID and based on the advanced method, whole exome sequencing (WES) to cover genes encoding receptors, ligands, and signaling molecules involved in B cell differentiation and maturation, such as but not limited to *ICOS*, *TNFRSF 13B* (TACI), *TNFRSF 13C* (BAFF-R), *TNFSF 12* (TWEAK), *CD19*, *CD81*, *CR2* (CD21), *MS4A 1* (CD20), *TNFRSF 7* (CD27), *IL21*, *IL21R*, *LRBA*, *CTLA4*, *PRKCD*, *PLCG2*, *NFKB1*, *NFKB2*, *PIK3CD*, *PIK3R1*, *VAV1, RAC2*, *BLK*, *IKZF1* (IKAROS), *IRF2BP2*, *BACH2*, and *STAT3*. The WES method will also enable to detect rare pathogenic variants related to complex CVID phenotypes.

Intriguingly, CVID shows high prevalence among all primary immunodeficiencies (PIDs), but despite recent advances in genomics and the ever-expanding spectrum of candidate genes, the overall diagnostic rate remains low, with pathogenic gene variants identifiable in merely 15% of patients. Furthermore, most patients with a diagnosis of CVID do not follow a classical Mendelian pattern of inheritance. It has been suggested that beyond the monogenic model of inheritance, another explanation of CVID origin is multifactorial, digenic, polygenic, and that epigenetic phenomena might show a causal relationship with the regulation of B cell development and functions. Among epigenetic factors, microRNA (miRNA) play a pivotal role in the regulation of expression of genes involved in the development and functiona maturation of B cells and therefore, deregulation of miRNAs might contribute to imparment of the immune response and antibody deficiency. While there is no single gene for CVID, in all the childen studied, an investigation of miRNA expression using lymphocyte-specific miRNAs profile will be performed.

The innovative aspect of the study relies on investigating not only a molecular genetic background underpinning the development of pediatric CVID but also on studying an epigenetic regulation of miRNA expression in children affected with CVID. It must be highlighted that such complex genetic-epigenetic studies with immunophenotype correlations have not been hitherto carried out in children affected with CVID.

Evaluating epigenetic miRNA dysregulation will serve for the future developments of patient-centered individualized diagnostic biomarker approach in pediatric CVID. It will also enable to define prophylactic measures and early-life interventions to alleviate the course of the disease and reduce the risk of its complications. The ultimate perspective for pediatric CVID is the administration of novel drugs that could act as therapeutic epigenetic modifiers of miRNA effect on specific gene expression.