Histological, clinical, laboratory and genetic predictors of patient outcomes with Henoch-Schönlein purpura and nephritis

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About the project

This summer, I worked as a research assistant in the lab of Prof. Marija Jelušić at the Medical School in Zagreb and University Hospital Center Zagreb. I worked on a Croatian Science Foundation project titled 'Histological, clinical, laboratory and genetic predictors of patient outcomes with Henoch-Schönlein purpura and nephritis', which is a 4 year long project encompassing dozens of research papers on this topic. More specifically, I assisted Dr. Jelušić's mentee Dr. Mario Šestan on his ongoing doctoral research paper, 'Contribution of the whole exome sequencing in the identification of genetic variants associated with childhood-onset systemic lupus erythematosus and IgA vasculitis'.

Although Henoch-Schönlein purpura (HSP) is most commonly a self-limiting disease and lasts on average up to 4 weeks, according to research, up to 60% of children with HSP develop nephritis. Nephritis is the main cause of morbidity and mortality in children with HSP. In the case of nephritis, there is a probability of developing chronic renal failure, which ranges from 1 to 15% and is highest in the first 6 months of disease. Although it is the most common vasculitis in children, with an incidence of 13-20 patients per 100,000 children, there are many unanswered questions and dilemmas, ranging from the diagnosis of the disease through prognosis to the choice of therapy with insufficiently clarified issues of etiopathogenesis, early determination of disease severity and the duration of the autoimmune process and the early diagnosis of the disease. Renal biopsy is important to confirm the diagnosis of HSPN, select therapy, and monitor patients, but there is still no single histological classification.

Given the above, as part of a national multicenter study, the project aims to determine which of the most commonly used pathohistological classifications best predict the severity and outcome of renal disease while finding the best classification model. On the other hand, kidney biopsy is an invasive procedure with certain complications, and great efforts are being made to find less invasive markers that can predict which patients will develop HSPN, have a poorer prognosis, and require more aggressive treatment procedures. Through detailed research, potential biomarkers have been identified (Gd-IgA1, HMGB1, calprotectin, protocadherin-1 and thiols) whose applicability in predicting the development of nephritis and the duration of kidney disease the project plans to determine. Furthermore, this study will determine the possible association of HMGB1 and RAGE gene polymorphisms and HSPN development, determine HMGB1 expression and the degree of macrophage infiltration in renal tissue, and identify HLA-DRB1 alleles that occur with a higher frequency in patients with Croatian population and the applicability of sequencing the whole exome in patients with HSP or HSPN will be determined. Analysis of genes and biomarkers in the serum, urine and stool of children with HSP, which indicate a prolonged duration of the autoimmune process and are an early predictor of renal impairment, will allow the isolation of patients with unfavorable course of the disease to find a strategy to prevent progression to end-stage renal disease.

Objectives

Hypothesis:

Using whole exome sequencing (WES) in carefully selected patients with cSLE and HSP and in the family members of affected individuals it is possible to **identify novel and rare gene variants** that may be contributing to etiopathogenesis of these diseases and expand existing genetic databases, which will represent a small but important step towards understanding the complex pathophysiology of the two diseases.

General aim:

- to identify *novel genes and variants* involved in cSLE and HSP

Specific aims:

- to identify individuals and families with a likely monogenic cSLE and HSP according to inclusion criteria and to obtain appropriate DNA samples from consented family members

- to perform WES in selected individuals

- to analyze exome sequencing data to identify genetic variants in all individuals sequenced

- to predict the pathogenicity of putative variants by comparison with exome sequencing data and using prediction tools

- to characterize and define possible mode of inheritance of the variants

Research plan
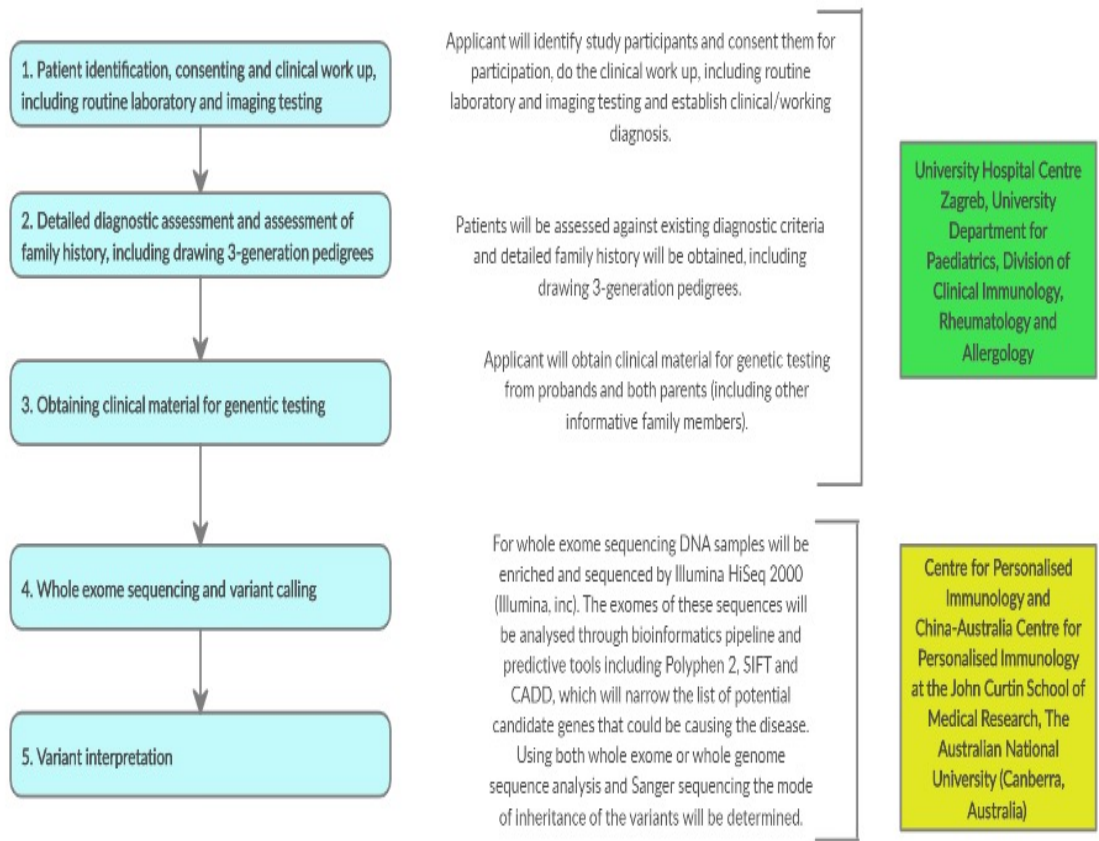
My contribution

- Statistics and data processing
- Sorting patient database information
- Conducting literature reviews
- Creating posters for Europaediatrics Congress 2021 in Zagreb, Croatia

My responsibilities on this project were diverse. I started out by doing literature reviews of articles which were relevant to the project, so I searched databases such as PubMed and Web of Science for papers related to paediatric IgA vasculitis. Later on, as I got more involved with Dr. Šestan's doctoral paper, I would analyze patient information from hospital databases and calculate relevant statistics. I also created two posters for the 2021 Europaediatrics Congress in Zagreb, for the papers *Determining the effectiveness of systemic immunomodulatory therapy in the treatment of patients with juvenile idiopathic arthritis associated uveitis depending on the chosen outcome measures* and *The impact of systemic immunomodulatory therapy on the intraocular inflammation and the need for topical glucocorticoid therapy in patients with juvenile idiopathic arthritis-associated uveitis*. I would also assist Dr. Šestan with translating documents from Croatian to English.

During my internship, I gained valuable knowledge and insight into clinical research. I am very grateful for the experience, particularly because I was able to work in the field of paediatric research, which I am especially interested in.

References

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