„There is no disease so rare that it does not deserve attention"
is one of the mottos that appear in the header of the portal for rare diseases, *Orphanet.* One look at the statistics to prove that this statement is justified:
There have been more than 6000 orphan diseases described so far. About 300 million people worldwide are affected by one of them, which makes up for more than 4% of the general population. Despite the scale of the problem, we still know very little about many of those diseases. The main problem here is the diversity of the diseases, and of course their rarity. In order to investigate one of those diseases, researchers are not seldom faced with the difficulty of a limited access to a representative group of patients with the disease of interest.
By definition, an orphan disease is one that occurs in less than 1 per 2000 people. Multiple endocrine neoplasia type 1 (MEN1), which is the main player of the presented project, is found in 2-3 per 100.000 people. This means that in Poland, there are over 1000 people affected by the disease; altogether, the disease is present in 200.000 people all over the world.
Irrespective of how rare the disease, for many affected people it can be a matter of life or death, how much is known about "their" disease and what can be done for them in their individual clinical case.

What do we know about MEN1 syndrome?
It is known that this syndrome is characterized by the simultaneous occurrence of tumors of the anterior pituitary gland, the parathyroid glands, pancreatic islets (making up the classical "P-triad"), and the adrenal glands, as well as neuroendocrine tumors. Additionally, non-endocrine malignancies may occur, which include angiofibromas, collagenomas, lipomas, leiomyomas and meningiomas. What is not known is which of the possible symptoms will appear in a given patient, at which age the disease will manifest, and how fast it will progress.
Also known is the reason of the disease, i.e. mutations in the *MEN1* gene, which are inherited in an autosomal dominant fashion. This means that the disease will develop in any individual who inherited a mutation in the *MEN1* gene. The problem is that despite the plethora of described cases, it was not possible to correlate the type of mutation with the clinical outcome of patients. Therefore, what we do not know is: Why, having the same mutation in the same gene, one person will manifest with a benign disease, whereas in the other patient the disease has a rapid progression, leading to the patient's soon death? Why do different tumors develop in patients from the same family (bearing the same mutation)?

What is the aim of the project?
To undertake the first feasible step which will hopefully bring us nearer to the answers to these questions, we designed the current study. Its authors, workers of the Medical Department of the Jagiellonian University Medical College, based on available literature, suggest a role for the genetic "background" of the patient. In other words: harmless, omnipresent genetic variations that determine the variety of people, in connection with a pathogenic *MEN1* mutation are suggested to play the role of so-called "genetic modifiers", which may drive the disease outcome in genetically predisposed patients.
The presented project is a pilot study and does not aim to give a final answer to the above raised questions. It aims to verify, whether indeed we may find the reason for the dissimilarities among MEN1 phenotypes in the patients' genetic predisposition. Only if this hypothesis can be confirmed, it will be reasonable to undertake deeper investigations searching for an answer to the given questions.

What do we want to do?
For the need of the project we want to read all coding sequences of the genomes from chosen MEN1 patients. Coding sequences carry information about the functioning of an organism. The proper collation of results will allow us to find common regions in genomes of people with the same disease phenotype, which at the same time will differ in people with distinct phenotypes. Such analyses are possible thanks to bioinformatics methods. We do not expect to reveal a single gene, but rather a map of multiple points in the human genome, which – when analyzed simultaneously, will prove to be associated with a given phenotype of MEN1 syndrome.

Why do we think this makes sense?
The MEN1 gene is expressed in all tissues of the organism, and its product, a protein called menin, is a so called tumor suppressor, which means that it has an anti-tumor effect, as long as it is not mutated itself. Menin interacts with plenty of other proteins, and in this way it participates in pathways which ensure a healthy cell genetic stability and the proper regulation of cell divisions. Taking into account the abundance of menin interactions with different proteins, and the diversity of pathways it is involved in, as well as the fact that we are still in the process of uncovering the functions of menin, it is very likely that small variations in other genes, which are harmless to a healthy organism, may modulate these interactions, and that many other factors exist which we have not yet discovered.

There is more and more prove in the research that the variations which "accompany" *MEN1* mutations may have an important impact on disease outcome. In a recently published paper, one potential genetic modifier for MEN1 syndrome has been suggested, which has been chosen for investigation based on available research data. As for now, there are but no published studies which would comprehensively scan the genome in order to search for genetic modifiers.
One of the reasons may be the rarity of the disease mentioned at the beginning. Scientific centers have a limited access to patients, or else, because of the lack of contact with the disease, they are not interested in its investigation. On the other hand there is the still limited access to appropriate analytical methods, especially for healthcare centers which do not specialize in scientific work. Together, these two reasons may be a serious obstacle in planning and performing this kind of investigations.

Are we able to realize the project?
The Jagiellonian University Medical College can overcome these problems. Access to a representative group of patients is warranted by the fact that it is settled in the structures of the University Hospital in Krakow, which is a reference center for

treatment of endocrine disorders, among others. The methodological and equipment background is warranted by the Genetics Laboratory of the Endocrinology Department, as well as by the OMICRON facility, which has been established at the JU MC some years ago.

It is a matter of time when also other centers in Europe and beyond will start to carry out screenings of the genome, searching for regions which might be responsible for the observed diversity of MEN1 phenotypes. We do have appropriate possibilities, therefore we want to make the first step, which will place hopes in patients and their physicians for a better understanding of their complaints, and thus, in further future, maybe it will be possible to implement individualized diagnostic and therapeutic procedures.