Arterial hypertension is a serious, yet modifiable, risk factor for various cardiovascular diseases in humans. It is defined as an increased level of systolic and/or diastolic blood pressure, which is caused by various environmental (e.g. obesity, smoking, lack of physical inactivity) and genetic factors.

Essential hypertension is a genetically complex disease, that is, its development depends on the activity and interaction of many genes. Currently, changes in the DNA sequence (so-called genetic polymorphisms) in approximately 1000 genes have been significantly correlated with blood pressure level in humans. Since the sequence of DNA is essentially unchanged during human life, the relationship between the above-mentioned genetic polymorphisms and blood pressure is considered causal, which means that the genetic polymorphism causes the change in blood pressure in the human body, and not the other way around.

The above example of causal inference can be translated into other clinical parameters or biomarkers that are at least partially heritable. Moreover, using Mendelian randomization analysis it is possible to check whether a given heritable parameter (e.g. the level of a specific amino acid in the blood) is causally correlated with a given disease, e.g. hypertension or ischemic heart disease. When the appropriate assumptions are met, the Mendelian randomization analysis allows one to draw causal conclusions regarding the correlation between two heritable parameters, which enables to determine the direction of the relationship, e.g., increased amino acid level may contribute to the development of arterial hypertension. These conclusions are necessary for clinical interpretation, especially since the level of many biomarkers changes as a result of the development of a given disease.

The aim of the presented project is to characterize specific amino acids that contribute to changes in blood pressure levels in humans. The project includes modern and comprehensive methods from the field of epidemiology, genomics, and molecular biology. The proposed research plan assumes Mendelian randomization analyses on well-selected and powered human cohorts. Importantly, the identified relationships between amino acid level and blood pressure will be verified in laboratory tests, including cell cultures and *in vivo* experiments.

The dynamically developing field of high-throughput profiling of the human genome, as well as biomarkers (proteins, amino acids, lipids, carbohydrates, etc.) present in human tissues, makes causal inference, using appropriately selected and verified statistical tools, a reliable and promising field of scientific research. This will contribute to the identification of biomarkers that not only respond to a disease or a given clinical condition, but constitute their causal factor. In the end, this will allow for a more accurate profiling of people in terms of the risk of a given disease, as well as a more accurate selection of the appropriate therapy.

Overall, the proposed project will identify specific amino acids as biomarkers that are causally related to blood pressure and related clinical parameters (e.g. arterial stiffness, endothelial function, ischemic heart disease), which may contribute to unravelling new molecular mechanisms of arterial hypertension and more accurate identification of people at increased risk for this disease.