Schizophrenia is a psychiatric disorder affecting approximately 24 million people worldwide – or about 1 in 222 adults. It is a psychotic disorder characterized by the presence of hallucinations and delusions – called "positive symptoms" – and by the progressive social withdrawal, reduced motivatin and cognitive decline – called "negative symptoms". Although it is not as common as other mental disorders, it often leads to considerable disability in all areas of life, including personal, social, educational and occupational functioning. The discovery of antipsychotic drugs in the 1950s brought a revolution in the management of patients with schizophrenia, but not all patients respond well to available medicines. In fact, only 1 in 4 patients achieves complete functional and clinical recovery. This is largely due to the fact that the underlying pathophysiology of schizophrenia is still not entirely clear.

We know that about 50% of the risk for developing schizophrenia is due to genetic factors. However, unlike some genetic disorders like hemophilia, schizophrenia cannot be attributed to mutations in one specific gene. In fact, recent genome-wide association studies found over 100 mutations contributing to the overall risk in small and not entirely understood ways. This prompted scientists to study the ***epigenetic risk factors associated with schizophrenia.***

The word "epigenetic" refers to all heritable mechanisms that can influence the expression of a gene, but are not caused by the changes in DNA sequence. These mechanisms include various modifications of the histone proteins, such as acetylation, or modifications of the DNA molecule, such as methylation. Those modifications do not change the underlying DNA sequence, but can silence or activate genes through changes to chromatin structure, or the way in which DNA is "packed" in the nucleus (among other mechanisms). Another epigenetic mechanisms – one that is the focus of this study – is RNA interference mediated by microRNAs (miRNAs). miRNAs are a family of small, non-coding RNA segments about 22 nucleotides long. They form complexes with specific proteins in the cytoplasm and bind with complementary mRNA strands, blocking the translation of proteins or destroying the target molecule. There are thousands of different miRNAs, and many studies examined their expression in the blood and brain of individuals with schizophrenia. We used a combination of a systematic literature search and bioinformatics analysis to select miRNAs that are likely to be relevant in schizophrenia. We narrowed our search to just 2 miRNAs, called miR-181b-5p and miR-34a-5p, and discovered that they are likely to target genes related to synaptic transmission, neurodevelopment and apoptosis.

We hypothesize that the increased activity of those miRNAs might cause neuronal cell death and impair processes related to synaptic transmission, possibly contributing to the pathogenesis of schizophrenia. To test our hypothesis, we developed a series of experiments.

First, we will grow human neuron-like cells obtained from a cell bank and artificially increase or decrease the activity of chosen miRNAs in their environment. This will allow us to examine the biological effects those miRNAs have on the way the cells grow and on the synapse-related proteins they produce. Additionally, we will also test if the antipsychotic drug clozapine, usually administered to patients with treatment-resistant schizophrenia, can block some of those effects.

However, we would also like to verify this hypothesis in the brains of individuals with schizophrenia. To gain a non-invasive "window to the brain", we will take blood samples from volunteers and use them to isolate extracellular vesicles that have been released by neurons and crossed the blood-brain barrier. This method has been used to measure the levels of various biomarkers of Alzheimer's disease without the need for a cerebrospinal fluid draw. We will use those vesicles to measure the expression of chosen miRNAs and the concentration of all proteins contained within them. We will also compare those results with various factors, such as the severity of schizophrenia symptoms or the use of antipsychotic medications. The overall goal of our project is to better understand the molecular processes underlying schizophrenia and we do not expect to achieve any immediate therapeutic breakthroughs. However, we believe that research such as this will contribute to the development of new treatment strategies in the long run.