What will this project study?

The main goal of this project is to **find genetic factors that determine how individuals respond to treatment with antidepressants.**

Why is this an important issue?

Today, 4.4% of the world's population suffers from depression. This debilitating disease is known to have a large genetic component and is treated mostly with antidepressants. Unfortunately, only a third of patients experiences any improvement while on their first drug and many people discontinue their treatment due to side effects. Scientific studies have shown that if we personalise the choice of antidepressant, condition of up to 70% of patients will significantly improve. One of the ways we can personalize antidepressant prescriptions is by developing genetic tests that will match the best drug for a given patient. In order to do this we need to know which genes to test and which particular genetic mutations (called variants) to look for. This problem has been studied for several decades and we now know that variants in two genes (called *CYP2D6* and *CYP2C19*) are important for how people metabolise and respond to antidepressants. We also know that there are many more genes involved in this process and we have identified around a 100 candidate genes, but what is their role in determining individual responses to antidepressants is unclear. As the important mutations may be quite rare, very large groups of people need to be investigated and many impactful variants have not yet been discovered.

How will we study genetics of antidepressant response?

In this project we will use a resource available to researchers around the world: the UK Biobank. It contains anonymized health-related data from 500 000 participants including genetic sequences, information on the medications they have been prescribed and on any medical diagnoses they received. Using these data we will conduct many analyses. Firstly, we will analyse ~30 000 available samples and describe genetic profiles in the set of ~100 candidate genes that may be important for antidepressant response. We will then compare these profiles between people that did take any antidepressants and two distinct control groups: healthy and depressed controls. Then we will try to investigate if any specific variants (or sets of variants) make individuals more prone to experience antidepressant toxicity. Poisonings with antidepressants are rare and there is an idea that they may be associated with particularly damaging genetic variants that are still unknown. Lastly we will try to investigate what are the genetic differences between people that respond well to antidepressants and those who don’t. To distinguish the non-responders we will look for individuals who, for instance, have tried multiple distinct antidepressants. We will compare variants in the candidate genes between these non-responders and responders and then try to classify samples to each group based only on genetic sequences.

What do we expect to discover?

Firstly, the initial comparisons will provide a foundation for research on genetics of antidepressants for us and other researchers. If we discover rare genetic variants that predispose individuals to antidepressant poisoning, it may help to identify genes and gene regions important not only for these rare severe adverse drug reactions but most probably also for more common side effects. Finally, if we attain the goal which is to build a model that predicts whether a given person will respond well to a particular drug we may contribute knowledge that will eventually lead to the development of the much needed personalisation of depression treatment.