Project 4

Project title: Determining the genetic mechanisms of cognitive responses to antipsychotic drugs
Lead group: Francesco Papaleo, IIT
Partner group: Daniel Zerbino, EMBL-EBI

Rationale: Cognitive and social deficits in psychiatric and neurodevelopmental disorders are currently considered society's main source of disability, having the most critical impact on the daily life of the patients and their relatives, on public health and long-term outcomes. Psychiatric and neurodevelopmental disorders such as schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), and bipolar disorder are characterized by a strong genetic component, with a high degree of genetic correlation among them, and a robust correlation with cognitive/social dysfunctions. Antipsychotics are first-line drugs for the management of these disorders, however clinical responses, especially for cognitive and social deficits, are highly variable with more than 30% of non-responders. No biomarkers exist to implement effective personalized treatments and genetic analyses are therefore not used in treatment choices. Moreover, the mechanistic bases of the unpredictable variability of treatments effects is unknown.

Aims: We propose to implement more efficient and biologically-supported personalised medicine strategies for cognitive/social alterations relevant to psychiatric and neurodevelopmental disorders. To overcome the inherent limitations of human studies such as genetic and clinical heterogeneity, gene-gene interactions, inconsistent diagnoses, and the limited access to functional mechanisms, we will use a combination of human genetics and studies in mice.

Objectives: 1. We will perform a genome-wide association study (GWAS) to screen a large set of genetic variants, which might be different between antipsychotics responder and non-responder patients. For this, we will use a large cohort of patients with psychiatric and neurodevelopmental disorders we already collected within the IIT based on their qualitative and quantitative clinical responses to antipsychotics, avoiding categorical diagnostic definition and covering all subjects exposed to these drugs. The results will then be associated by tissue-specific co-localisation to genes using the eQTL Catalogue resource and Post-GWAS pipeline at EMBL-EBI, to associate phenotypes to gene expression shifts.
2. We will use our behavioral/mechanistic tools developed in mice, which we previously demonstrated to have high translational value in the context of cognitive and social processes from mice to humans, and from humans to mice. The aim is to better address the mechanisms underlying genetic-based variability in drug responses. This knowledge will pave the way to the development of more efficient and biologically-supported personalized healthcare for cognitive and social deficits relevant to psychiatric and neurodevelopmental disorders.

Integration of expertise of partners: Francesco Papaleo will contribute access to his human datasets, genetically modified mouse models and in vivo mechanistic tools (i.e. optogenetics, fiberphotometry, miniscopes etc), and the Next-Generation Sequencing Facility of the IIT of Genova. Daniel Zerbino will contribute expertise in the querying of GWAS and functional databases at EMBL-EBI and elsewhere, as well as statistical analysis of genetic data. He will ensure that access to resources such as Ensembl, GWAS Catalog or eQTL Catalogue is seamless.