A precision medicine genetic marker for core cognitive deficits in schizophrenia

1)Scheggia D. 2)Mastrogiacomo R. 3)Mereu M. 4)Sannino S. 5)Straub RE. 6)Armando M. 7)Managò F. 8)Piras F. 9)De luca MA. 10)Weinberger DR. 11)Spalletta G. 12)Papaleo F.

Istituto Italiano di Tecnologia

Schizophrenia is an heterogeneous disorder affecting more than 25 million people worldwide and characterized by a strong genetic component. Antipsychotics are currently the first-line and most largely used medications for the management of schizophrenia spectrum and other psychotic disorders. While these drugs generally ameliorate positive symptoms, clinical responses for negative symptoms and cognitive impairments are non-optimal and highly variable. Notably, cognitive deficits are considered the main source of disability, having the most critical impact on public health and long-term outcomes. Because of the clinical heterogeneity and high therapeutic variability, guidelines strongly recommend adapting antipsychotic treatments to each individual case. However, no biological rationale still exists to implement more effective and personalized healthcare in schizophrenia. Similarly, the mechanisms underlying the unpredictable variability to antipsychotics effects are unknown. Here we found a pharmacogenetics interaction in schizophrenia core cognitive dysfunctions. In particular, results from patients with schizophrenia and genetically modified mice indicated that genetic variations reducing dysbindin-1 conferred better executive control responses to antipsychotics. By lentiviral vector-mediated microRNA silencing manipulations, we demonstrated that in vivo the antipsychotics-by-dysbindin-1 interaction mechanistically relied on dopamine D2 receptors functioning within the medial PFC. Furthermore, we established that this pharmacogenetics effect resides in the functional enhancement of D2 intracellular trafficking in carriers with reduced levels of dysbindin-1 only following the treatment with antipsychotics. These findings highlight a genetic indicator for the implementation of personalized medicine for cognitive disabilities in schizophrenia based on a concrete biological mechanism.