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Pharmacogenomics of antidepressant drugs: perspectives for the personalization of treatment in depression

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PHARMACOGENOMICS OF ANTIDEPRESSANT DRUGS: PERSPECTIVES FOR THE PERSONALIZATION OF TREATMENT IN DEPRESSION

Chiara Fabbri

SUMMARY

Depressive disorders affect more than 300 million people globally and are the third cause of disability worldwide. Genetic variants were demonstrated to explain a relevant proportion of variance in antidepressant response. The aim of this dissertation was to contribute to the identification of genetic markers that can be used to develop personalized antidepressant treatments, improving disease prognosis.

Different strategies were combined to achieve this purpose. Candidate genes implicated in antidepressant metabolism (cytochrome 2C19 or CYP2C19) or pharmacodynamics (e.g. FKBP5, CHL1) were investigated in terms of individual effect on treatment outcomes but also in terms of the molecular pathways through which they may play a role in antidepressant action. In addition to pathway analysis, the role of exomic variants as predictors and treatment-resistant depression (TRD) as phenotype were considered particularly promising since they were overlooked in previous studies.

Few candidate genes show potential clinical usefulness to guide antidepressant treatment when considered individually and CYP2C19 is one of these genes. Pathway analysis provides the potential of explaining a higher variance in outcomes than the study of single genes and help in clarifying the mechanisms of antidepressant action. The involved pathways include those mediating inflammation (e.g. B-cell receptor and steroid hormone signaling), neural plasticity and neurogenesis (e.g. regulation of chromatin structure). The inclusion of both common and rare variants in pathway analysis may allow the detection of signals that would be otherwise missed.

Current clinical applications of antidepressant pharmacogenetics are based on single candidate genes only. The current frontier is to develop polygenic predictors that can have a higher effect size compared to single genes as well as develop predictors of specific phenotypes such as TRD. This dissertation identified pathways that can be the starting point for further pharmacogenetic studies but can also serve to identify new pharmacological targets.