

Key Roles of the Treatment Response in Major Depressive Disorder, Genetics, and Gut Microbiome

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DESCRIPTION

Depression is a disease with complex pathogenesis, from endogenous genetic factors to external environmental factors that impact the occurrence and treatment of depression. The heritability of Major Depressive Disorder (MDD) has been confirmed in previous studies, and large Genome-wide Association Study (GWAS) results have reported high-risk loci for MDD. All these laid the foundation for better exploring and using genetic factors of depression to help clinical diagnosis and treatment. An increasing number of studies have confirmed the relationship between gut microbiota and depression or other psychiatric disorders, including the regulation of oxidative stress, tryptophan metabolism, kynurenine pathway, or metabolic processes. Meanwhile, the microbiota-gut-brain axis could also help explain the link between gut microbiota and abnormal brain function. There are also many reports of using gut microbiota which are used to treat depression and psychiatric disorders. The combination of genetic risk factors and the key gut microbiota information associated with MDD can be used to predict the different response groups after treatment, which can better help patients improve depressive symptoms clinically. The prediction of these two phases of the two-week and eight-week responses can help explain in depth the changes in response mechanisms during the dynamic course of depression treatment.

Romboutsia has been proposed as an important biomarker to differentiate MDD from healthy controls and has been proposed as a candidate trigger or etiology of MDD in children and adolescents. A significant difference in the abundance of *Romboutsia ilealis* was observed between the 8-week response group and the non-response group, but not at the 2-week time point. This suggests that the core microbiota has dynamic changes during the treatment of depression, and may have different indicator roles at different time points. The RUFY3 gene is associated with neuronal polarity and could explain MDD through methylation or axon elongation. A significant difference

in rs58010457 at RUFY3 between responders and non-responders was reported at 2-week interval, but not at 8-week interval. This suggests that the long-term accumulation of depressive episodes or natural growth processes can influence the early stages of treatment. However, in the later stage of treatment, the difference may not be significantly observed due to various confounding factors. These two examples suggest that genetic factors and gut microbiota may play different roles at different stages of depression treatment.

To better use genetic information and gut microbiota information to help clinical prediction of treatment response, artificial intelligence or machine learning methods are necessary. The machine learning method verified that the contributions of genetic information and gut microbiota information to the prediction results differed at different times. Genetic information contributed more to the prediction of the 2-week response, while information related to gut microbiota contributed more to the prediction of the 8-week response. This suggests that gut microbes have irreplaceable and important long-term treatment functions. In general, it may take longer to improve depressive symptoms by improving the composition of the gut microbiota, which may be related to how the gut microbiota affects depressive symptoms, including by affecting secreted metabolites, the immune system, and processes related to the endocrine and neuronal systems. The interaction with drugs is also one of the possible reasons for the lagging effect of microbiota. Complex drug-microbial relationships can affect drug bioavailability and bioactivity as well as toxicity.

The in-depth study of the differences in biomarkers at different time points, combined with machine learning and artificial intelligence, can help to better understand the dynamic changes of genetic factors and gut microbiota during the treatment of depression. More detailed observation of the dynamic changes and importance judgment can help researchers understand the spatiotemporal polymorphism of the complex gut microbiota and the host.

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