

Press release

Treatment-resistant depression identified as a distinct molecular subtype

- ***An international study published in Brain, Behavior, and Immunity shows that patients with treatment-resistant depression (TRD) have a unique biology, different from those who respond to standard therapies.***
- ***More than 5,000 genes were found to behave differently in TRD compared with non-resistant patients.***
- ***The study reports the first results of the PROMPT consortium, which aims to combine clinical and molecular data using machine learning to predict which patients are at risk of developing TRD.***

Barcelona, October 31st, 2025. – A study led by the Hospital del Mar Research Institute, the University of Brescia, and the Paris Brain Institute, with the collaboration of partners in the PROMPT consortium coordinated by the University of Münster, provides evidence that **treatment-resistant depression (TRD) is not just a more severe form of major depression, but a biologically distinct condition.**

TRD is a severe condition characterized by chronic and recurring depressive symptoms that often do not improve after several treatment attempts. To understand why some patients respond to antidepressants and others don't, researchers analyzed blood from 300 patients with major depressive disorder and discovered that more than 5,000 genes behave differently in TRD compared with non-resistant patients. ***"Many of these genes are linked to the immune system, regulation of gene activity, and neuroplasticity, all key to the biology of depression"*** explains Dr. Marie-Claude Potier of the Paris Brain Institute. ***"The fact that around 20% of active genes, including many key to depression pathophysiology, behave differently, points to TRD having its own underlying biology."***

Most standard antidepressants are known to modulate immune factors. The **reduced immune response observed in TRD patients suggests that this could be the reason why these pharmacological treatments often fail in these patients.** ***"Recognizing this can guide the development of new, more targeted therapies"*** adds Dr. Alessandra Minelli, psychologist and associate professor at the University of Brescia.

A step closer to precision psychiatry

This study reports the first results of the PROMPT consortium—funded by the European ERA PerMed scheme—which aims to build machine-learning models to predict patients at risk of developing TRD. ***"These results open the door to a new molecular understanding of depression and give us the opportunity to rethink how we classify and treat patients,"*** notes Dr. Júlia Perera Bel, from the Biomedical Informatics Research Programme (GRIB) of the Hospital del Mar Research Institute and Pompeu Fabra University. ***"We are now studying other biological entities, such as small RNA molecules and genetic mutations, to have a comprehensive molecular characterization of these patients"***. Dr. Anna Sirés, first author of the study and also researcher at GRIB, adds that by combining the findings from multiple molecular layers, they expect to **capture the biological complexity and multifactorial nature of the disease.**

PROMPT is a proof of concept study that can lay the groundwork for molecular testing and machine learning algorithms in psychiatric diseases. ***"This study is a step towards precision psychiatry, where algorithms could help decide the best treatment for each patient"***

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and avoid unnecessary treatments,” remarks Prof. Bernhard Baune, coordinator of the PROMPT consortium from the University of Münster.

Reference article

Blood transcriptomic analysis reveals a distinct molecular subtype of treatment-resistant depression compared to non-treatment resistant depression. *Brain, Behavior, and Immunity*, November 2025. DOI: [10.1016/j.bbi.2025.106103](https://doi.org/10.1016/j.bbi.2025.106103)

More information

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