Medical Xpress

International study completes the largest genetic map of psychiatric disorders so far

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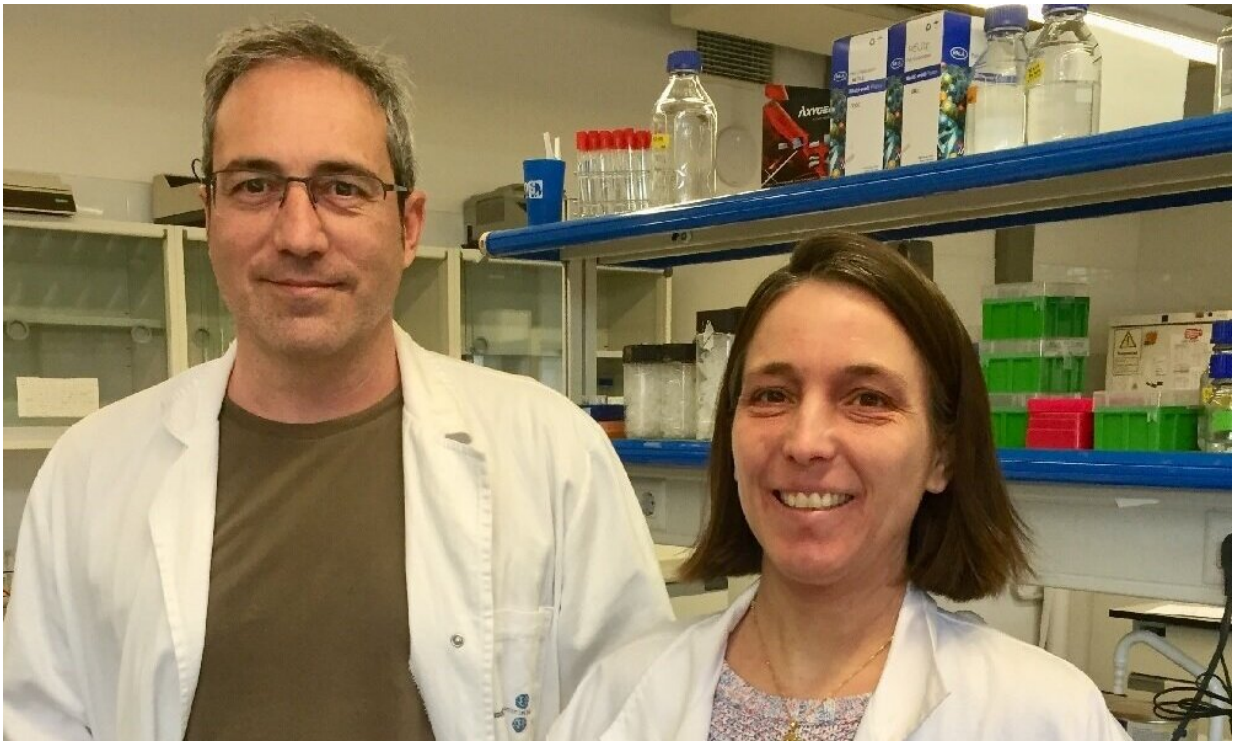

The experts Bru Cormand and Raquel Rabionet, from the Faculty of Biology and the Institute of Biomedicine of the UB (IBUB). Credit: UNIVERSITY OF BARCELONA

An international study published in the journal *Cell*, has described 109 genetic variants associated with eight psychiatric disorders: autism, ADHD, schizophrenia, bipolar disorder, depression, obsessive-

compulsive disorder and Tourette syndrome, in a total of about 230,000 patients worldwide.

Among the participants in the new study, the most ambitious and detailed study published so far on the genetics of psychiatric disorders, are the researchers Bru Cormand and Raquel Rabionet, from the Faculty of Biology and the Institute of Biomedicine of the University of Barcelona (IBUB), the Research Institute Sant Joan de Déu (IRSJD), the Rare Diseases Networking Biomedical Research Centre (CIBERER), and Marta Ribasés, Josep Antoni Ramos-Quiroga and other members of the research group in Psychiatry, Mental Health and Addictions of the Vall d'Hebron Research Institute (VHIR) and the Mental Health Networking Biomedical Research Centre (CIBERSAM).

The international study is promoted by the Psychiatric Genomics Consortium, the most ambitious international platform on genetics of psychiatric conditions, and is led by the expert Jordan W. Smoller, from Harvard University (United States). Apart from listing potential genetic predisposition and resilience factors of pathologies, this study determines the specific genes that the pathologies share, and completes the genetic map of psychiatric disorders.

A new genetic perspective on psychiatric disorders

About 25% of the world population is affected by some type of psychiatric disease that can alter intellectual ability, behavior, affectivity and social relations. The new study, based on 230,000 patients and 500,000 controls, analyzes the genetic base shared by eight psychiatric pathologies and defines three groups of highly genetically related disorders: Those that respond to compulsive behaviors (anorexia nervosa, obsessive-compulsive disorder); mood and psychotic disorders (bipolar disorder, major depression and schizophrenia) and early-onset neurodevelopmental disorders (autism spectrum disorder, ADHD and

Tourette syndrome). In this context, the VHIR team participated with a sample of 500 adult people with ADHD and 400 healthy controls.

"Those disorders listed in the same group tend to share more genetic risk factors between them than with other groups. Moreover, we saw that these groups built on the basis of genetic criteria match with the clinical output," notes Bru Cormand, professor at the Department of Genetics, Microbiology and Statistics and head of the Neurogenetics Research Group at the UB.

"However, the new study does not put emphasis on the genes shared by members of a particular group, but on the genes shared by the highest number of disorders," continues Cormand. "That is, those factors that would somehow give way to a 'sensitive' brain, more likely to suffer from any psychiatric disorder. And the fact that this could be one or another disorder would depend on specific genetic factors, not forgetting about the environmental factors."

Many psychiatric disorders show comorbidities—they tend to co-occur, sometimes in a sequential manner. Therefore, it is quite likely for a patient to show more than one disorder over his/her life.

According to the results, a gene related to the development of the nervous system, DCC, is a risk factor for all eight studied disorders. Also, the RBFOX1 gene, which regulates the splicing in many genes, is involved in seven out of the eight disorders. In addition, ADHD and depression share 44% of those genetic risk factors that are common in the general population. These figures reach 70% for schizophrenia and bipolar disorder. Antoni Ramos-Quiroga says, "These results help people with ADHD to understand the disorder, and also why they can suffer from depression more frequently. Furthermore, this is a new scientific evidence that ADHD can persist over life, and be present in adults. We hope this helps to reduce the social stigma regarding ADHD and the

other mental illnesses."

"We now know this situation regarding psychiatric disorders can be explained, in part, by genetics. Therefore, regarding the case of someone with ADHD, we can estimate the genetic risk to develop other disorders s/he does not suffer from yet—for instance, drug addiction—and take preventive measures if the risk is high. However, these predictions are just probabilistic and not fully deterministic," notes the researcher.

Expression of risk factors in psychiatric disorders

Apart from genomics, the study focuses on the analysis of functional aspects of the genetic risk variants. For instance, the impact on gene expression in space (which organs, specific regions of the brain, tissues and even cells do express the disease genes) and in time (in what developmental phase of the individual these activate). Moreover, it analyzes the genome at a tridimensional level to detect potential relations between risk genetic variants and distant genes.

One of the most relevant findings of the study is that those genes that are risk factors for more than one disorder—genes with pleiotropic effects—are usually active during the second trimester of pregnancy, coinciding with a crucial stage in the development of the nervous system.

Oddly enough, some genetic variations can act as genetic risk factors in a certain disorder but they have a protecting effect in other cases. Lecturer Raquel Rabionet says, "In the study, we identified 11 areas of the genome in which the effects are opposed in different pairs of disorders—that is, protection in one case, and susceptibility in the other. This could make sense in some instances in which there would be a genetic variant with contrary effects in ADHD—a disorder usually related to obesity—and anorexia.

"However, regarding the neurodevelopmental disorders such as autism and schizophrenia, there are genetic variants with opposite effects and others that work in the same direction. This suggests that the genetics of psychiatric disorders is more complex than what we thought and we are still far from solving this puzzle," says Rabionet.

Hereditary genetics versus environmental factors

Alterations in a single DNA nucleotide—single nucleotide polymorphisms (SNPs)—explain less than a third of the genetics of these pathologies. The other two-thirds may correspond to other types of genetic changes, such as rare variants, which are not that common in the human genome.

"Psychiatric disorders have a multifactorial origin," note the experts. For instance, thanks to studies with twins we know ADHD has a 75% genetic load and the remaining 25% would be explained by environmental factors (traumatic experiences during childhood, exposure to toxins, etc.)".

"This panorama could be expanded to the other psychiatric disorders we studied, because the contribution of genetics is generally higher than 50% and SNPs would always explain less than a half of this percentage. That is, SNPs have an important weight but there are many factors yet to be explored," note Cormand and Rabionet, who—as part of the study—worked on the group of patients with ADHD, anorexia or obsessive-compulsive disorder in Catalan hospitals.

Exploring new frontiers of human genetics

The study published in the journal *Cell* broadens the horizon of knowledge of a previous study (*Nature Genetics*, 2013), promoted by the

Psychiatric Genomics Consortium on a base of 32,000 patients and 46,000 controls and five disorders (autism, ADHD, schizophrenia, bipolar disorder and depression). The conclusions of the new article improve on those of the previous study, which analyzed the shared genetics of mental disorders with a global perspective but did not point at specific genes.

In the future, one of the priorities of the consortium will be to complete the genetic landscape of mental disorders through the analysis of other genetic variations—for instance, the variations of the number of copies or CNVs—that affect large DNA segments. From an epigenetic perspective—in particular the methylation of DNA—they want to analyze the interactions between genes and environment, which could be decisive in psychiatry.

"It will be important to understand how genetic alterations are translated to the phenotype—the disorder—and this involves studying the function of every single gene identified in the genomic studies (using animal or cell models). In any case, the objective is to use genetics to improve and customize the diagnosis, prognosis and therapy of these pathologies which may be highly disabling for the affected people," note Bru Cormand and Raquel Rabionet.

More information: Phil H. Lee et al, Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders, *Cell* (2019). DOI: 10.1016/j.cell.2019.11.020

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