Unexpected mental illnesses found in a spectrum of a rare genetic disorder

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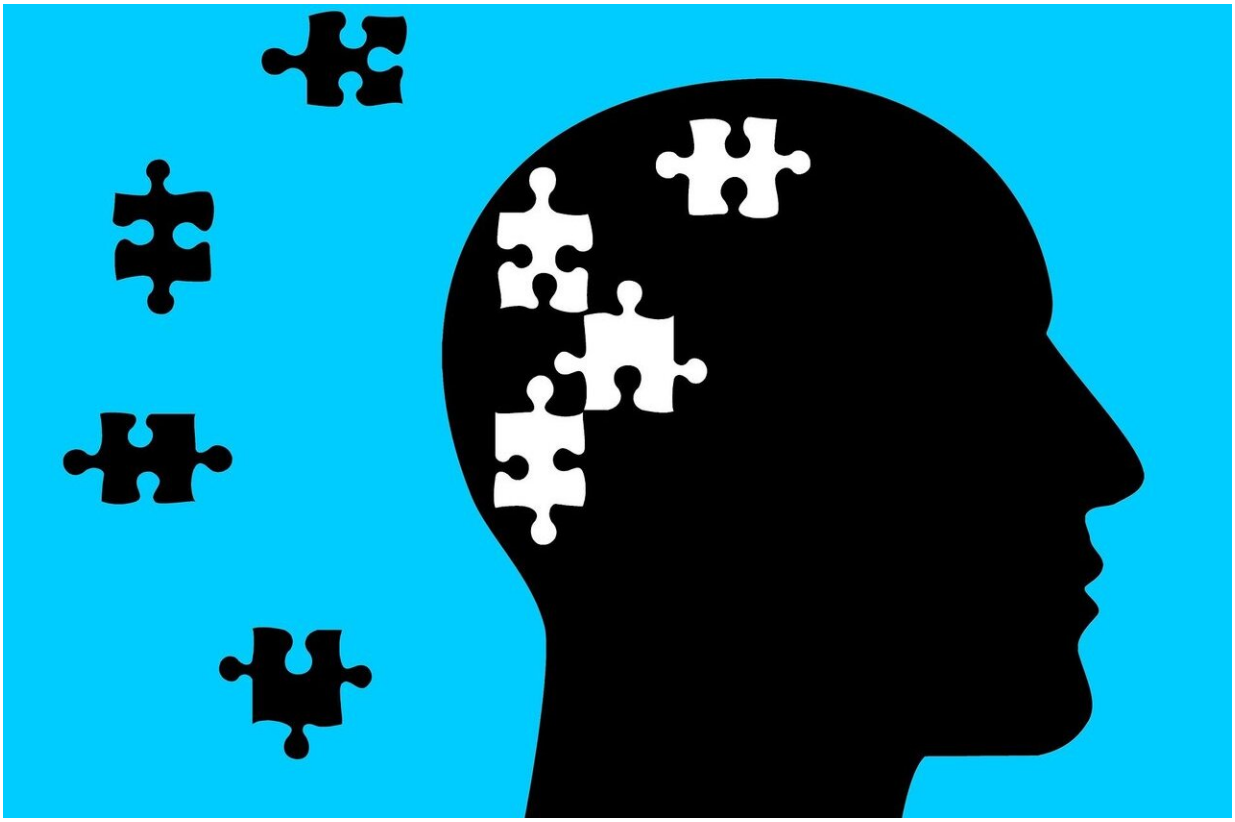

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UC Davis MIND Institute researchers found an unexpected set of mental illnesses in patients with a spectrum of a rare genetic disorder. Their study revealed the need for clinicians to consider the complexities of co-

existing conditions in patients with both psychological and fragile X associated disorders.

Double-hit fragile X spectrum cases

The patients had a "double-hit" condition that combined features and symptoms of fragile X syndrome and premutation disorder.

Fragile X syndrome (FXS), a rare single-gene disorder, is the leading inherited cause of intellectual disability. It is caused by a lack of the fragile X mental retardation protein (FMRP) resulting from a change, called mutation, in the FMR1 gene.

In most people, the CGG section of the FMR1 gene is repeated between 10 to 40 times. In some rare cases, individuals have premutation disorder when their FMR1 gene has 55 to 200 CGG repeats. When this section expands to over 200 repeats, there is a full mutation in the gene. This full mutation causes an inability to produce FMRP and leads to FXS.

The study presented 14 cases of male patients with FMR1-gene mutations and a variety of psychiatric disorders. These patients, ages ranging between nine and 58 years, had features resembling FXS and symptoms common among premutation carriers.

FXS symptoms include hand flapping, hyperactivity, recurrent ear infections, severe anxiety and tantrums. Individuals with FXS frequently have speech and language delays, behavior challenges and symptoms of autism spectrum disorder (ASD).

Premutation, on the other hand, is associated with the development of neurological problems associated with aging. One example of such age-related problems is Fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS is a disease characterized by progressively severe

tremor and difficulty with walking and balance. Premutation is also associated with medical and psychiatric problems such as migraines, hypertension, sleep apnea, restless legs syndrome, anxiety and depression.

Neurological and developmental problems

The study found that patients with premutation had a much earlier onset of neurological problems. Some even had earlier symptoms of neurodegeneration, particularly if they had developmental delay or ASD during their childhood. They also showed trouble with their emotional processing.

"Lower levels of FMRP can cause a range of emotional processing issues," said Andrea Schneider, associate research scientist in the Department of Pediatrics and at UC Davis MIND Institute and the lead author on the study. "Some of the common emotion-related disorders we found are mood disorders, anxiety and psychotic features."

The researchers called for more studies on the association of psychosis and lower FMRP levels—especially in patients with a double hit condition. The case series also highlighted the need for clinicians to consider additional possible diagnosis for FMR1 mutations in psychiatric patients.

"Clinicians need to be aware of the physical and mental toll on patients with a FMR1 mutation who also show symptoms of psychosis or early onset of neurological problems," said Paul Hagerman, professor of biochemistry and molecular medicine at UC Davis and co-author on the study. "This understanding helps develop treatment plans that address the multiple needs of these patients."

The study, titled "Elevated FMR1-mRNA and lowered FMRP – A

double-hit mechanism for psychiatric features in men with FMR1 premutations," appears in the latest issue of the journal *Translational Psychiatry*.

More information: Andrea Schneider et al, Elevated FMR1-mRNA and lowered FMRP – A double-hit mechanism for psychiatric features in men with FMR1 premutations, *Translational Psychiatry* (2020). DOI: 10.1038/s41398-020-00863-w

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