Possible genetic triggers of autism symptoms and motor issues identified for several rare diseases

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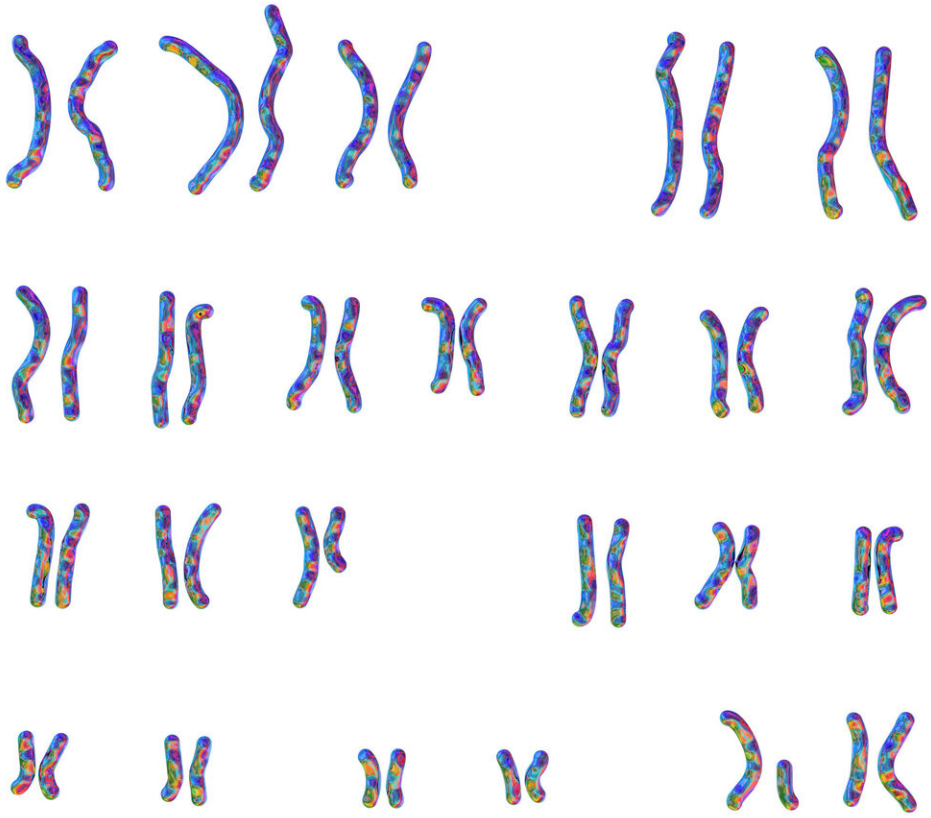

Credit: Kateryna Kon

New research on the genetics of Prader-Willi and Angelman syndromes could help in developing personalised therapies for associated mental illness and autism features. Prader-Willi syndrome (PWS) and Angelman syndrome (AS) have few treatments for associated complications including autism spectrum disorder (ASD) and mental health issues such as psychosis.

Murdoch Children's Research Institute (MCRI) and University of Kansas Medical Center (KU Medical Center) experts have found that changes in expression levels of the UBE3A gene in white blood cells were associated with social and communication difficulties in PWS and impairment of fine motor and language skills in AS. The team now plan to investigate whether these changes are also seen in patients' supporting brain cells, called glia.

PWS and AS each affect 1 in 15,000 people and among other things cause intellectual and behavioural challenges. Apart from giving human growth hormone, treatments for Prader-Willi syndrome only address individual symptoms. The only Angelman syndrome treatments involve symptom-related therapies such as anti-seizure medication and physical, communication and behaviour therapy.

Published in *Translational Psychiatry*, the study investigated three conditions caused by chromosome 15 alterations, and included 27 participants affected with PWS, 21 with AS and 10 with chromosome 15 duplication (Dup15q) syndrome. It identified new links between UBE3A gene activity in white blood cells, autism features and fine motor and language skills. These raise the possibility that inflammatory pathways may be involved in contributing to disease severity in these conditions.

Senior author, MCRI Diagnosis and Development Laboratory head and University of Melbourne Department of Paediatrics Associate Professor David Godler, said immune system changes had been implicated as key

contributors to mental health issues in other disorders, including ASD. This study now suggests this may also be the case in chromosome 15-related conditions.

If confirmed in future studies, these findings could lead to new treatments that control the function of immune cells. They could also lead to new ways of predicting the type and severity of symptoms, using easily accessible biological materials, such as blood, which may be helpful for families and in assessing the effectiveness of new treatments as they arise.

"The immune system plays an important role in ensuring that nerve cells in the brain function properly," Associate Professor Godler said. "This is the first study to show that gene expression changes in white blood cells of individuals with PWS and AS are related to these issues too."

Australian study clinical lead Professor David Amor said the new research made meaningful change possible. "For a child that has significant obsessions, behavioural disturbance or autism, even if we can just improve those by 20 percent, that can potentially translate into a substantial improvement in quality of life both for the child and for the family," he said.

Project psychologist Dr. Emma Baker said psychiatric and behavioural issues associated with these conditions were "quite challenging". Those with PWS are prone to emotional outbursts, communication issues, and restrictive and repetitive behaviours that can exacerbate the core features of the disorder, such as overeating.

"This can really interfere with how an individual with Prader-Willi engages with the world," Dr. Baker said. "Motor difficulties are big issues for children with Angelman syndrome. We found associations between UBE3A gene expression levels in white blood cells and fine

motor skills. Improving motor skills can improve engagement and learning."

The study was conducted in collaboration with University of Kansas Medical Center PWS expert Professor of Psychiatry and Paediatrics Merlin Butler and his group, primarily supported by US-based Foundation for Prader-Willi Research (FPWR), Foundation for Angelman Syndrome Therapeutics (FAST) Australia and the Medical Research Future Fund.

"The study approach was novel," Professor Butler said. "The resultant genetic and clinical findings are preliminary; but if confirmed may revolutionise our understanding of brain-behavioural-gene interactions, opening new research on the role of genetics in human behaviour and treatment."

The principal investigators on this project have now been awarded additional funding from the US-based Foundation for Prader-Willi Research (FPWR) to build upon its findings by examining brain tissues of individuals affected with PWS.

FPWR Director of Research Programs Dr. Theresa Strong said, "These novel insights … lay the groundwork for exploring new treatment approaches for some of the most challenging aspects of PWS. Autism features, behavioural problems and mental illness can have profound impacts on individuals and families."

Ms Sally Hartmanis has a sister, Stephanie, with Angleman syndrome. "It's been extremely difficult to never hear Stephanie speak and to have no way of knowing what she is thinking or experiencing, or how much she understands. Over the years, Stephanie has developed certain repetitive behaviours which can be quite distressing to witness. It's upsetting not knowing what the cause of these behaviours are, or how we

can help her.

"I'm comforted by the knowledge that researchers are finding and putting together the puzzle pieces underlying this heartbreaking condition."

More information: Emma K. Baker et al. Relationships between UBE3A and SNORD116 expression and features of autism in chromosome 15 imprinting disorders, *Translational Psychiatry* (2020). DOI: 10.1038/s41398-020-01034-7

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