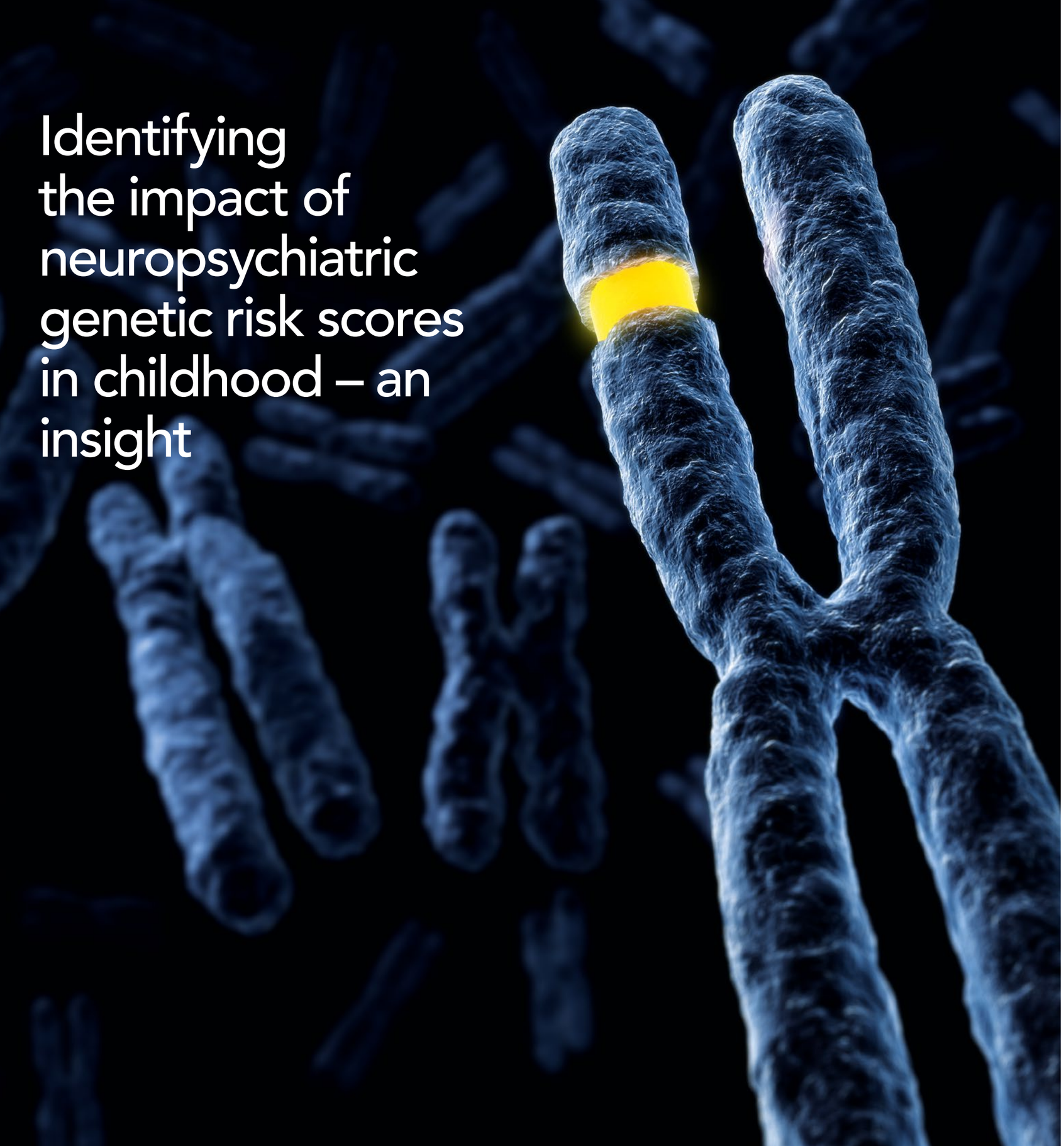
# Identifying the impact of neuropsychiatric genetic risk scores in childhood – an insight



Certain alleles (variants of our genes) can indicate an increased likelihood of developing a particular psychiatric disorder. These 'risk alleles' and the total number of them present may also have an effect on general neurodevelopment in childhood. **Dr Lucy Riglin**, along with her colleagues at Cardiff University, is exploring the impact of these genetic risk scores. Her work may help to change the way that child neurodevelopmental problems are approached and add to our understanding of mental illness.

Mental disorders affect one in four people at some point in their lives, with 450 million patients worldwide currently suffering from such a condition. Globally, mental illness is projected to cost $6 trillion per year by 2030. Therefore, it is crucial that preventative measures are developed.

For many complex diseases, we have a good understanding of early risk processes within the general population during childhood that may contribute to disease development. Dietary and lifestyle risks, for example, are strongly associated with coronary heart disease. This knowledge is vital for informing development of targeted public health strategies aimed at reducing the risk of developing disease later in life. In contrast, early risk processes that may influence development of mental disorders are poorly understood. Late presentation of illness, heavy reliance on retrospective ('in-hindsight') patient reports and a lack of biological tests for mental conditions all hinder development of early management and treatment.

Step in Dr Lucy Riglin and colleagues. By exploring the contribution of genetic risk variants to mental illness in the general population, the team aim to better identify early risk processes for mental illness.

**UNLOCKING THE ORIGINS OF MENTAL ILLNESS**

As part of the Child and Adolescent Psychiatry and MRC Centre for Neuropsychiatric Genetics and Genomics research group at Cardiff University, Dr Riglin defines and assesses common genetic variants or "alleles" from very large studies of patients with illnesses that appear to be risk factors in mental disorders.

Much of the focus of her research tests what effect these risk alleles have on childhood development and mental health in a healthy population. This may in the future offer clues toward identifying the early risks for mental disorders, as has been done for other complex diseases.

**SCHIZOPHRENIA: EARLY INDICATORS OF INCREASED RISK**

Numerous mental illnesses, such as schizophrenia, are highly heritable. Although they typically start after puberty, they may be preceded by childhood problems. A recent study led by Dr Riglin set out to examine the relationship between schizophrenia risk alleles and early childhood developmental impairments. Among some of the early developmental issues experienced by those who go on to develop schizophrenia are cognitive and social as well as mood and behavioural problems.

Polygenic risk scores or PRS, represent an individual's total number of risk alleles. PRS are being used as useful measures of genetic liability for different disorders. Dr Riglin and her colleagues have identified a connection between schizophrenia PRS with behaviour, learning ability, mood, social and other impairments in young children (pre-puberty). Importantly, the team's work proposes that

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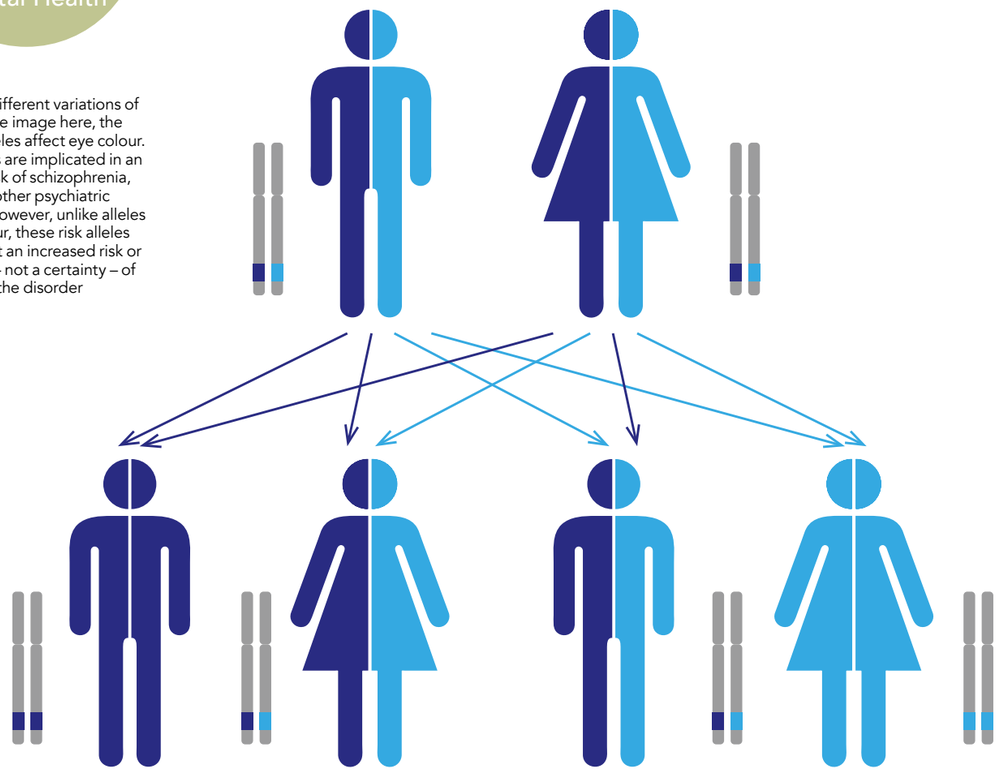

Alleles are different variations of a gene. In the image here, the different alleles affect eye colour. Some alleles are implicated in an increased risk of schizophrenia, ADHD and other psychiatric disorders. However, unlike alleles for eye colour, these risk alleles only suggest an increased risk or probability – not a certainty – of developing the disorder

these problems could be early indicators of a genetic liability to schizophrenia. In addition, the study suggests that these schizophrenia liability traits may be present from the age of just four years old.

**ADHD: UNRAVELLING THE DETERMINANTS OF SYMPTOM PERSISTENCE**

Attention Deficit Hyperactivity Disorder (ADHD) is another disorder which has a strong inherited component. The condition is common in children, in whom symptoms such as hyperactivity, inattention and impulsivity can decline over time. Yet in roughly 65% of cases, symptoms continue into adulthood. Until now, the determinants of symptom persistence and decline have been poorly understood. Investigating the connection between genetic risk (indexed by PRS) and developmental trajectories of ADHD symptoms from childhood to puberty, Dr Riglin shows that an increased ADHD PRS is linked to persistence of ADHD symptoms into adulthood, within the general population.

Two key groups of individuals were identified as having a high probability of initially elevated ADHD symptoms in childhood – of these, an estimated 40% showed persistence of symptoms with increased ADHD traits at 17 years, compared to 60% whose ADHD traits were limited to childhood. Uniquely, the study also suggests that ADHD persistence can be associated with 'multi-morbidity' (the presence of multiple disorders) including lower IQ, behaviour problems, social issues and language impairments. Given that multi-morbidity was more common for those with persistent compared to childhood-only ADHD symptoms, this finding has clinical relevance since it may help identify potentially persistent ADHD. Importantly, it also suggests that multi-morbidity deserves more attention than received so far, particularly since there is a need to improve the prediction value of current clinical diagnoses.

**THE IMPACT OF MENTAL DISORDER RISK ALLELES ON CHILDHOOD NEURODEVELOPMENT**

Working with researchers Anita Thapar, Michael O'Donovan, Stephan Collishaw, Ajay K Thapar and Barbara Maughan, Dr Riglin's latest project examines PRS across childhood neurodevelopmental and mental health areas. Importantly, the research group is also interested in examining what happens over time (longitudinal studies) to see whether polygenic risk scores can be linked to increased or declining symptoms / trajectories of mental health symptoms. The team also raise the need to investigate the effect of environmental factors in relation to the development of mental illness and assessment of neurodevelopmental issues.

Further work is needed but this is certainly an exciting area for development that will help us to better understand mental illness, how it may develop especially early on in life, and, ultimately, identify opportunities for prevention.

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## Q&A

***Which other neurological or mental health issues are you interested in potentially exploring?***

There are several other areas that our group are interested in exploring, including other mental health disorders, such as depression. We are also interested in using polygenic risk scores to investigate traits such as irritability, that are involved in a range of different mental health problems.

***In what way could your research guide prevention strategies?***

By helping to identify childhood characteristics that share genetic links with mental health disorders, our work aims to aid understanding of the possible ways illnesses develop. Where we have found evidence suggesting that specific childhood characteristics are associated with genetic links to mental health disorders, it is possible that these characteristics will be useful either to monitor as possible indicators of increasing signs of risk, or as targets for prevention. However, it is important to stress that much work is needed to investigate the potential benefit of monitoring/targeting these characteristics. As with many physical health problems, most people who have these risk factors will not go on to develop a disorder, so research is needed to better understand when and for who these characteristics might be useful to monitor/target.

***How did you become involved in researching genetic risk scores in mental disorders?***

I am really interested in how mental health problems develop – this is very complex and involves lots of different factors, including both genetic and environmental risks. I think genetic risk scores are an exciting research tool because they allow us to investigate broad genetic risk in a relatively simplistic way.

***What are the key challenges in this area of research?***

One challenge in our research is how specific findings are. Currently polygenic risk scores for mental health disorders are associated with lots of different childhood characteristics (e.g., schizophrenia risk scores are associated with social and behaviour problems), and childhood characteristics are also associated with polygenic risk scores for multiple disorders (e.g., childhood behaviour problems are associated with polygenic risk scores for both schizophrenia and ADHD). This can make understanding the ways illnesses develop complicated. Another issue is causation, as it is difficult to differentiate risk factors (characteristics that occur before a disorder) from causal factors (risk factors that if we successfully manipulated would reduce the chance of a disorder), which is important when considering prevention strategies.

***Do you think that PRS could become a diagnostic tool? Why or why not?***

Genetic risk scores for mental health disorders currently have very low predictive validity and should not be used for diagnostic purposes. Mental health problems are complex and this is reflected in the diagnostic process, which requires a clinician to incorporate a range of information including symptoms, how they affect day-to-day life and clinical history.

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## Detail

**RESEARCH OBJECTIVES**

Dr Riglin's work investigates the impact of genetic risk scores for mental disorders (identified from patient studies) on specific neurodevelopmental domains measured in childhood (in the general population), including emotional regulation, cognition, social communication and behaviour.

**FUNDING**

Medical Research Council (MRC)

**COLLABORATORS**

Anita Thapar, Michael C O'Donovan, Stephan Collishaw and Ajay K Thapar (Cardiff University), Barbara Maughan (King's College London).

**BIO**

Dr Lucy Riglin is a researcher at Cardiff University where she helps to identify the early impacts of genetic risks. She hopes to guide future understanding of how mental illnesses develop.

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