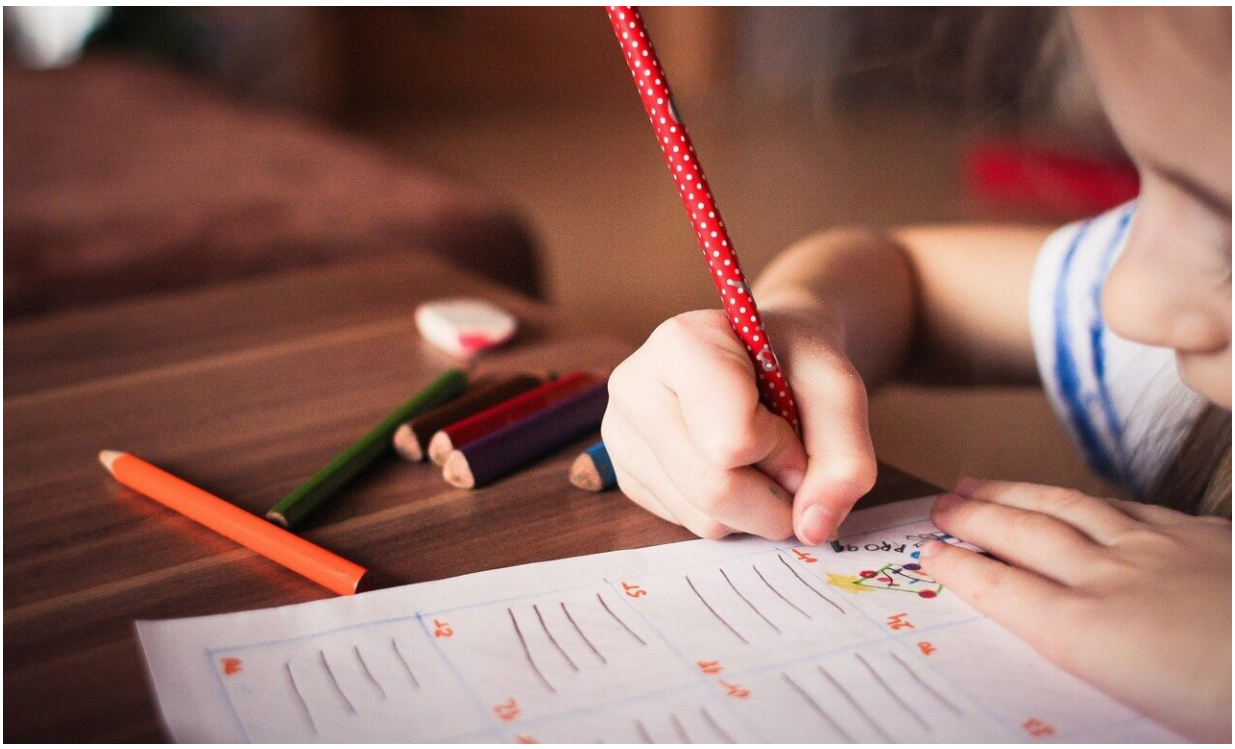
Diagnoses of developmental, behavioral, and mental health problems more likely for children with rare genetic disorders

August 2 2022



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A major study of children with intellectual disabilities has highlighted the additional challenges that they often face, including a much-increased likelihood of being diagnosed as autistic, as well as Attention

Deficit Hyperactivity Disorder (ADHD) and other mental health difficulties.

With the advent of rapid whole genome sequencing, children presenting with an intellectual disability or developmental delay are recommended to have their DNA sequenced to identify the underlying genetic cause.

To capitalize on this recent NHS development, researchers at the University of Cambridge, University College London and Cardiff University established IMAGINE ID, a national UK cohort study that aims to discover how genetic changes affect children and young people's behavior, in order to inform better care of families and children now and in the future.

Writing in *The Lancet Psychiatry* today, the researchers have published the results of an analysis of data from almost 2,800 young people with rare genomic variants—changes to their DNA—that are associated with intellectual disability.

Professor Lucy Raymond from the University of Cambridge, the study's senior author, said, "Thanks to all the families that have taken part in our research, we've been able to conduct the largest study to date of the impact of rare genetic variants associated with intellectual disability. What we've found from parents is that these children are extremely likely to develop other neurodevelopmental or mental health conditions, which can present additional challenges both to the children and their families."

All the participants were aged between 4 and 19 years. Just under three-quarters (74%) had an intellectual disability caused by a duplication or deletion of sections of DNA—a so-called copy number variant (CNV). The remaining young people had a disability caused by a single "spelling error" in their DNA—a change in the A, C, G or T

nucleotides—referred to as a single nucleotide variant (SNV).

Compared to the English national population, children in the study were almost 30 times as likely to have been diagnosed as autistic. In the general population, 1.2% of people are diagnosed with the condition compared to 36% of the study participants. Similarly, 22% of the study population was diagnosed with ADHD, compared to 1.6% of the general population, meaning that they were more than 13 times more likely to have the condition.

Around one in eight children (12%) had been diagnosed with oppositional defiant disorder, in which children are uncooperative, defiant, and hostile toward others—a rate 4.4 times higher than in the general population.

One in ten (11%) had an anxiety disorder, a 1.5 times increased risk. Rates of childhood depression were significantly lower, at just 0.4% compared with 2.1% of the general population, but this may increase over the next few years as some mental health disorders do not start until later adolescence or early adult life. Almost all of the children (94%) were reported to have at least one significant physical health problem, including disturbed sleep (65%), motor or movement disorders (64%) or seizures (30%).

Dr. Jeanne Wolstencroft from Great Ormond Street Institute of Child Health, University College London, said, "Routine genomic testing now allows parents to understand the genetic cause of intellectual disabilities in an increasing number of children, but because so many of these conditions are rare, we still lack information on the impact this has on their children's future mental health.

"We already know that intellectual disabilities tend to be associated with an increased likelihood of neurodevelopmental conditions, as well as

emotional and behavioral difficulties, but we found that where there is an identifiable genetic cause, the likelihood is amplified considerably. This suggests that these children should be provided with early assessment and help where appropriate."

The team has also shown for the first time that children with intellectual disability caused by a genetic variant inherited from a family member are more likely to come from a more deprived socioeconomic background. This suggests that some parents or family members with the same variant may also have unrecognized difficulties that placed them at a social and educational disadvantage. These children were more likely to be diagnosed with a neuropsychiatric condition and were also more likely to exhibit behavioral difficulties.

Professor David Skuse from Great Ormond Street Institute of Child Health, University College London, said, "We hope this work helps improve the targeting of assessments and interventions to support families at the earliest opportunity. We'd like to see better training for health care providers about the wider use and utility of genetic testing. We have identified its potential value in terms of prioritizing children with mental health needs for child mental health services, who are currently hugely limited in the UK."

More information: Neuropsychiatric risk in children with intellectual disability of genetic origin: IMAGINE—The UK National Cohort Study, *The Lancet Psychiatry* (2022). DOI: 10.1016/PIIS2215-0366(22)00207-3

Provided by University of Cambridge

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