JOURNAL
OF THE CANADIAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY / DE L'ACADÉMIE CANADIENNE DE PSYCHIATRIE DE L'ENFANT ET DE L'ADOLESCENT

RECOMMENDED ACADEMIC READING

Genetics

In this issue, RAR is focused on recent research articles in the field of genetics that relate to psychiatry. I thank our four genetic expert contributors for their identification of important papers and their informative summaries. At the end of the column find some additional references for papers by these experts. A special shout-out to one of our contributors, Dr. Louise Gallagher, who will be the new Chief, Department of Psychiatry at The Hospital for Sick Children (SickKids) in addition to other leadership positions.

John D. McLennan

Dr. Chad Bousman recommends an article by Ramsey and colleagues (1). This article reports results of a serial, cross-sectional study that collected data from 16 US health systems (~2.9 million pediatric patients) to assess the potential opportunities for genotype-guided prescribing in pediatric populations. Genotype-guided prescribing is a relatively new personalized prescribing strategy that is aimed at lessening the challenges associated with finding an appropriate drug and dose for an individual. The emergence of this strategy as a complement to existing strategies, such as therapeutic drug monitoring, has been facilitated by genotype-based prescribing guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) (2). Although the clinical uptake of genotype-guided prescribing in adult psychiatry is growing exponentially, in child and adolescent psychiatry uptake has been more modest due to knowledge gaps. In their study, Ramsey et al. addressed a critical knowledge gap by providing robust estimates of how often drugs with genotype-guided guidelines are prescribed in pediatric care settings. There findings suggest selective serotonin reuptake inhibitors are among the top drug classes that genotype-guided prescribing would have the greatest impact. Other drug classes included antiemetics and analgesics.

Chad A. Bousman, MPH, PhD
Associate Professor, Department of Medical Genetics, University of Calgary

Member Matheson Centre for Research and Education, Hotchkiss Brain Institute, and Alberta Children's Hospital Research Institute
Calgary, Alberta

References

1. Ramsey LB, Ong HH, Schildcrout JS, Shi Y, Tang LA, Hicks JK, et al. Prescribing Prevalence of Medications With Potential Genotype-Guided Dosing in Pediatric Patients. JAMA Netw Open. 2020;3(12):e2029411. https://pubmed.ncbi.nlm.nih.gov/33315113/
2. Relling MV, Klein TE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Caudle KE. The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. Clin Pharmacol Ther. 2020;107(1):171-5. https://pubmed.ncbi.nlm.nih.gov/31562822/

Dr. Louise Gallagher recommends an article by Rees and Owen (1). This review article presents the progress towards precision medicine in psychiatry. The article provides a review of genomic advances in psychiatry, considers the barriers to progress and sets out the required research agenda to progress the precision psychiatry objective. They highlight advances in our understanding of the genetic architecture of psychiatric disorders which although highly heritable are genetically complex due to large numbers of genomic variants that are implicated within and across disorders. This has progressed neurobiological understanding, e.g., synaptic dysfunction in schizophrenia. Acknowledging the challenges posed by polygenicity and pleiotropy (where the same variants are associated with different psychiatric outcomes) they discuss the steps required to advance translation within a precision medicine framework. For example, clinical stratification and risk prediction requires integration of genomic and other data. Mechanistic studies show promise for drug repurposing but polygenicity challenges the development of informative cell and animal models. To

address this, the near-term research agenda requires better integration of genomic and clinical data in larger and more diverse cohorts. Longitudinal data is required for outcome prediction and harmonized clinical data are required. Ultimately, multi-omics approaches will be necessary, but they argue that there exists an empirical platform to understand mechanisms and to identify and target new treatments for psychiatric disorders. Overall, the article provides an informative and accessible overview of the current state of genomics and the implications for precision psychiatry that is relevant to child psychiatry.

Louise Gallagher, MB, MRCPsych, PhD
Professor and Chair of Child and Adolescent Psychiatry
Department of Psychiatry
School of Medicine

Trinity College Dublin
Dublin, Ireland

References

1. Rees, E. and M. J. Owen. Translating insights from neuropsychiatric genetics and genomics for precision psychiatry. Genome Med.202;12(1): 43. https://pubmed.ncbi.nlm.nih.gov/32349784/

Dr. Jacob Vorstman recommends an article in Lancet Psychiatry, published in May 2021 by Varun Warrier and colleagues. The study is intriguing in that it addresses a highly relevant problem, childhood maltreatment, from a genetics angle. I suspect many readers may ask – like I did myself - how heritability can even be considered in something so intuitively "environmental". The study may be misconstrued as an endeavor to find "genes for child maltreatment", or worse, as indirectly assigning some fault to the child. To be clear, it is neither. Investigators attempted to elucidate the extent to which heritable child characteristics may modify environmental risk. As the authors explain, heritable factors may act *passively* (parental genetic makeup, transmitted to offspring, influences familial circumstances); *actively* (genetic makeup influences child behavioral traits), and *reactively* (child traits, influenced by genetic makeup, may elicit certain parental responses).

Their meta-analysis of over 185,000 individuals identified 14 genetic regions associated with maltreatment, and evidence for both active and reactive gene-environment mechanisms. Using Mendelian Randomization, a clever strategy that uses genetic correlations to infer causality between a risk factor and outcome, investigators found, amongst other relationships, that the probability of ADHD and schizophrenia in children showed both causal and consequential relations to maltreatment ("bidirectional"), while maltreatment increased the probability of depression ("unidirectional").

Why is this research relevant? Childhood maltreatment is a significant societal problem with numerous downstream negative consequences. A better understanding of the role of child characteristics and their genetic underpinnings, and how these interact with the environment to influence risk of maltreatment, may very well open up new avenues towards prevention. In their conclusion, the authors highlight "*the importance of familybased support strategies, targeting parents and their interaction with their children".* As JCACAP's readership knows all too well from systems theory, each member is essential; seen from that perspective it seems clear that the findings presented here are highly relevant.

Jacob Vorstman, MD, PhD
Child & Adolescent Psychiatrist
Associates Chair in Developmental Psychopathology
Hospital for Sick Children
Department of Psychiatry
University of Toronto
Toronto, Ontario

References

1. Warrier V, Kwong AS, Luo M, Dalvie S, Croft J, Sallis HM, Baldwin J, Munafò MR, Nievergelt CM, Grant AJ, Burgess S. Gene–environment correlations and causal effects of childhood maltreatment on physical and mental health: a genetically informed approach. The Lancet Psychiatry. 2021 May 1;8(5):373-86. https://pubmed.ncbi.nlm.nih.gov/33740410/

Also recommended is an excellent editorial comment on this work by Pezzoli & Saudino (2021)

Pezzoli P, Saudino KJ. Causes and consequences of childhood maltreatment: insights from genomics. The Lancet Psychiatry. 2021; 8(5), 348-349. https://pubmed.ncbi.nlm.nih.gov/33740411/

Dr. Paul Arnold recommended an article by Joo et al (2022) examines whether genome-wide polygenic risk scores (PRS) for 24 psychiatric and other common traits are associated with risk of suicide among preadolescent children. The authors also examined the interaction of polygenic risk with early life stress in predicting suicidal thoughts and behaviours in children. PRS scores were first constructed from publicly available genome-wide summary statistics (the "discovery" sample). The resulting PRS were then tested using machine learning methods in a target sample of just over 7,000 children (age 9 to 10) drawn from the large U.S. Adolescent Brain and Cognitive Development (ABCD) study. Specific PRS associated with the risk of suicide included PRS for ADHD, PTSD (positive associations)

and general happiness (negative association). The investigators also identified significant interaction between PRS for autism spectrum disorder and early life stress in predicting suicidality. I found this article interesting as it suggested the future utility of genetic risk models based on "big data" for predicting suicide, one of the most important clinical issues for child and adolescent psychiatrists. The study also demonstrated the potential added value of considering interaction between genetic and environmental risks like early life stress. An important limitation of this study, shared by most genomic studies, is that the data used to generate PRS largely comes from samples of people with European ancestry which could seriously limit the future utility of PRS for non-European patients unless the lack of diversity in human psychiatric genetic studies is addressed.

Paul Arnold, MD, PhD, FRCPC
Director, The Mathison Centre for Mental Health Research & Education
Alberta Innovates Translational Health Chair in Child and Youth Mental Health
Professor, Departments of Psychiatry and Medical Genetics
Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary
Calgary, Alberta

References

1. Joo YY, Moon SY, Wang HH, Kim H, Lee EJ, Kim JH, Posner J, Ahn WY, Choi I, Kim JW, Cha J. Association of Genome-Wide Polygenic Scores for Multiple Psychiatric and Common Traits in Preadolescent Youths at Risk of Suicide. JAMA Network Open. 2022 Feb 1;5(2):e2148585. doi: 10.1001/jamanetworkopen.2021.48585. https://pubmed.ncbi.nlm.nih.gov/35188556/

Article written by the contributors for readers to consider:

Bousman CA, Mukerjee G, Men X, Dorfman R, Müller DJ, Thomas RE. Encountering Pharmacogenetic Test Results in the Psychiatric Clinic. Can J Psychiatry. 2021:7067437211058847. https://pubmed.ncbi.nlm.nih.gov/34783587/

Davies RW, Fiksinski AM, Breetvelt EJ, Williams NM, Hooper SR, …& Vorstman J. Using common genetic variation to examine phenotypic expression and risk prediction in 22q11. 2 deletion syndrome. Nature medicine. 2020 Dec;26(12):1912-8. https://pubmed.ncbi.nlm.nih.gov/33169016/

Jessel, CD, Al Maruf A, Oomen A, Arnold PD, Bousman CA. Pharmacogenetic testing knowledge and attitudes among pediatric psychiatrists and pediatricians in Alberta, Canada. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 2022; *31*(1), 18. https://www.cacap-acpea.org/wp-content/uploads/Pharmacogenetic-Testing-Knowledge-and-Attitudes.pdf

Schaaf CP, Betancur C, Yuen RK, Parr JR, Skuse DH, Gallagher, L., ... & Vorstman JA. A framework for an evidence-based gene list relevant to autism spectrum disorder. *Nature Reviews Genetics*, 2020; *21*(6), 367-376. https://pubmed.ncbi.nlm.nih.gov/32317787/

Sinopoli VM, Erdman L, Burton CL, Park LS, Dupuis A, Shan J, Goodale T, Shaheen SM, Crosbie J, Schachar RJ, Arnold PD. Serotonin system genes and obsessive-compulsive trait dimensions in a population-based, pediatric sample: a genetic association study. Journal of Child Psychology and Psychiatry. 2019 Dec;60(12):1289-99. https://pubmed.ncbi.nlm.nih.gov/31321769/