Quantitative and molecular genetics of child and adolescent mental health disorders: Recent advances, knowledge gaps and directions for future research

Abstract
Quantitative and molecular genetic research studies have already contributed substantially to increase the understanding of the links and boundaries across different child and adolescent mental health conditions and between child and adult forms of psychopathology. Several findings have been replicated across quantitative and molecular genetic methods, and across clinical and population-based samples. An important task for future quantitative and molecular genetic research is to advance the understanding of how childhood psychopathology unfolds into adult forms of psychopathology, and to reveal the etiologic relationships across different forms of psychopathology. In the years to come, we can expect further breakthroughs in the genetics of child and adolescent mental health disorders to come from converging evidence across different quantitative and molecular genetic methods.

KEYWORDS
developmental psychopathology, mental health disorders, molecular genetics, quantitative genetics

Quantitative genetics
Many readers of JCPP Advances know that the key question of contemporary quantitative genetics of child and adolescent mental health disorders and traits is not “if” genetic factors are important, but rather “how” genetic factors influence different forms of child and adolescent psychopathology across development. Longitudinal quantitative genetic studies have over the past decades addressed important questions about the underlying genetic and environmental contributions to developmental trajectories of psychopathology. Most of these studies have explored development of these phenotypes from childhood to adolescence. The general pattern of findings indicate, if we put it simply, that both stable and dynamic genetic risk factors influence psychopathology over the developmental course from childhood to adolescence (Hannigan et al., 2017). The stable component of underlying genetic risks suggest that childhood and adolescent forms of psychopathology are genetically linked. The dynamic components suggest that the set of genetic variants accounting for the onset of psychopathology may differ from those accounting for the persistence and remission of psychopathology. An important task for future quantitative genetic research is to extend this research into adulthood to advance our understanding of how childhood psychopathology unfolds into adult forms of psychopathology. This is now possible given that several twin datasets (e.g., TEDS) were established about 25 years ago, and many of these data sources now contain detailed longitudinal assessments of psychopathology from early childhood via adolescence into adulthood.

Numerous bivariate quantitative genetic studies have, over the past decade, estimated genetic correlations between different mental health disorders (Martin et al., 2018). These findings generally support the hypothesis that many forms of psychopathology across the life-span correlate in part due to genetic factors. Findings from more recent multivariate quantitative genetic studies suggest that comorbidity across different forms of psychopathology is, at least in part, due to a genetically influenced general psychopathology factor (often referred to as the P-factor) (Lahey et al., 2011), as well as by genetic sharing across sub-dimensions of psychopathology (e.g., internalizing and externalizing problems). Important questions regarding the general factor of psychopathology and internalizing and externalizing sub-dimensions remain to be addressed, such as development from childhood and adolescence into adulthood. Increasing use of sophisticated multivariate quantitative genetic approaches has the potential to
generate a more in-depth understanding of the etiological (genetic and environmental) relationships underlying not just psychopathology, but also a broader disorder spectrum that includes physical conditions which frequently co-occur with psychopathology. Some aspects of these questions will be addressed in the first special issue of JCPP Advances, which is scheduled for late 2021 and will focus on the interplay between mental and physical health.

### Molecular genetics

Genome-wide association studies (GWAS) based on large samples of diagnosed cases and controls have been instrumental in identifying common genetic variants across the genome that influence mental health disorders. This method began to produce statistically significant results in psychiatry more than 10 years ago, in particular for mental health disorders with a typical onset in adulthood, such as schizophrenia. It was not until recently that statistically significant findings emerged from GWAS for major child and adolescent mental health disorders. For example, the latest GWAS findings from the ADHD Working Group of the iPSYCH and the Psychiatric Genomics Consortium (PGC), identified 12 loci significantly associated with ADHD (Demontis et al., 2019).

Findings from large-scale GWAS efforts and methods development (e.g., LD score regression) have allowed researchers to estimate genetic correlations between disorders to quantify the extent to which the genetic basis of different mental health disorders overlap.

GWAS from large case and control samples have generated critical new insights about the genetic correlations across a wide range of different mental health disorders, traits and behaviors. These results largely confirm prior findings from quantitative genetic findings, illustrating that some genetic risk is shared across different mental health disorders, even across disorders with a typical onset in childhood and those with a typical onset in adulthood (Demontis et al., 2019).

A key characteristic of more recent molecular genetic studies is that they, much like quantitative genetics, have moved from bivariate to multivariate approaches (e.g., genomic structural equation modeling). A recent cross-disorder publication represents an important example of how genomic multivariate approaches can be used to more clearly describe the genetic relationships across different forms of psychopathology. Findings supported three more specific mental health disorder clusters (i: Mood and psychotic disorders; ii: Disorders with compulsive behaviors; iii: Early onset neurodevelopmental disorders), characterized by strong genetic sharing (Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address & Cross-Disorder Group of the Psychiatric Genomics, 2019).

There is still a lack of genome-wide significant findings for many child and adolescents’ mental health conditions. Large-scale data collections and collaborative efforts are needed to secure statistical power for gene discovery. Decisions around different ascertainment and phenotyping strategies in GWAS of mental health disorders typically need to consider the costs, time, accuracy and the level of phenotypic detail. There has recently been an increased push for utilizing electronic health records for phenotyping in GWAS. Such an approach would not only increase sample size substantially, but also facilitate new research directions, such as studies of largely understudied childhood mental conditions and the biological basis of treatment response. The publication by Arrhenius et al. (2021) in this issue of JCPP Advances highlights the value of using electronic health records from national registers to ascertain a large number of individuals with a diagnosis of specific learning disorders (N = 3162).

GWAS of quantitative measures of mental health disorders from independent population-based cohort studies have so far been under-powered to detect genome-wide significant findings. Reducing phenotypic heterogeneity across different childhood samples will likely also be key in paving the way to future GWAS success in population-based cohort settings. Aggregation of data across several large-scale population-based cohort studies (e.g., EAGLE consortia) is one promising approach that has already contributed to the identification of genome wide hits, when combined with large-scale case-control data from consortia (e.g., PGC/iPSYCH ADHD) (Demontis et al., 2019). Another promising strategy for large-scale cohort studies again involves linkage to electronic health records. This approach has already been implemented in several ongoing cohort studies (e.g., the Swedish twin registry and the Norwegian Mother and Child Cohort Study). Complementing the detailed quantitative measures with information about clinical diagnosis not only for interesting research questions, but also facilitates collaboration with GWAS consortia of case-control samples.

Using summary statistics from large-scale GWAS, it is possible to calculate individual polygenic scores (PGS) in independent genotyped samples. This has opened up an important line of research using population-based samples with detailed, longitudinal psychopathology phenotyping. One important finding from these studies is that some genetic risk is shared between diagnosed mental health disorders and trait variation at the population level (e.g, ADHD) (Taylor et al., 2019). These results confirm quantitative genetic findings and indicate that psychopathology probably reflect the quantitative extreme of common genetic variants operating dimensionally throughout the full distribution of traits and symptoms. More longitudinal PGS research studies are needed to advance the understanding of developmental trajectories of psychopathology from childhood to adulthood. A recent PGS study of quantitative measures from several population-based cohort studies represents a useful example, with findings demonstrating that shared genetic factors exist between childhood psychopathology traits from age 6 years onwards and adult depression and associated traits (Akingbua et al., 2020).

It is important to highlight that the number of PGS studies has increased rapidly in recent years and clarity around methodology and interpretation of results is much needed, such as generalizability to individuals of non-European ancestry. Implementation of sophisticated study designs (e.g., within-siblings designs) and analyses (e.g., mediation analyses), coupled with larger and more diverse samples, have the potential to help uncover the mechanisms underlying identified PGS associations and improve clarity around interpretation.

### CONCLUSIONS AND FUTURE DIRECTIONS

Quantitative and molecular genetic research have already contributed substantially to an increased understanding of links and
boundaries across different child and adolescent mental disorders and between child and adult forms of psychopathology. Several findings are replicated across quantitative and molecular genetic studies. Triangulation of evidence across different study designs is an increasingly recognized approach to strengthen causal inferences of risk factors in epidemiological research. For example, the editorial perspective by Baldwin et al. (2021) in this issue of JCPP Advances describes how three different approaches (i.e., measurement comparisons, within-family comparisons, and cross-context comparisons) can be used to test the role of perceived versus objective experiences of childhood adversity in psychopathology. Other epidemiological risk factor studies have successfully triangulated evidence using within-family comparisons and Mendelian randomization methods (Liu et al., 2020).

An important task for future quantitative and molecular genetic research is to advance the understanding of how childhood psychopathology unfolds into adult forms of psychopathology. Genome-wide significant findings for more child and adolescents’ mental health disorders, as well as large-scale genotyped samples with longitudinal information on psychopathology, are critical for this endeavor. A better understanding of developmental trajectories is not only important for early onset neurodevelopmental disorders (e.g., ADHD), but also for mental health disorders with a typical onset in adulthood; as those emerge over time, with signs or symptoms developing in childhood, long before individuals typically receives a diagnosis and treatment. A better understanding of the biological basis of these early signs may help identify new treatment targets and high-risk groups.

Quantitative and molecular genetic studies have now moved from bivariate to multivariate approaches. Increased use of sophisticated multivariate statistical approaches has the potential to generate an even more detailed map of the etiologic relationships across different forms of psychopathology. A better understanding of the etiologic relationships is one important step towards improving the classification system of psychopathology and identifying shared mechanisms and pathways influencing across different types of psychopathology.

In the years to come, we can expect further breakthroughs in the genetics of child and adolescent mental health disorders to come from converging evidence across different quantitative and molecular genetic methods. There is, however, still a lack of clinical translation and more work is needed from this research tradition to truly fill its potential and in the future have a real impact for individuals with mental health disorders, their careers, and clinicians.

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