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Behavior and Molecular Genetic Approaches to Comorbidity

Erik G. Willcutt, PhD

University of Colorado Boulder, Professor of Psychology and Neuroscience, Director, *Eunice Kennedy Shriver* NICHD Colorado Learning Disabilities Research Center, Director of Clinical Training, Faculty Fellow, Institute for Behavior Genetics, Faculty, Center for Neuroscience, Department of Psychology and Neuroscience, 345 UCB, University of Colorado Boulder, Boulder, CO 80309

Abstract

Purpose of Review: This review provides an overview of studies that used behavioral genetic methods to understand the genetic and environmental influences that lead to comorbidity, the co-occurrence of two or more developmental disorders in the same individual.

Recent Findings: Comorbidity is primarily explained by shared genetic influences for most pairs of disorders that have been studied, including attention deficit hyperactivity disorder (ADHD) and learning disabilities, conduct disorder and ADHD, anxiety and depression, and anxiety and autism spectrum disorder (ASD). Molecular genetic studies indicate that the etiologies of developmental disorders are highly multifactorial, with dozens or even hundreds of genes acting in combination with environmental risk factors to lead to each individual disorder and the extensive comorbidity between disorders. Due to this complexity, current state-of-the-art studies are now combining molecular genetic data from multiple large samples to begin to achieve adequate statistical power to identify the specific genetic polymorphisms that lead to comorbidity.

Summary: An extensive literature demonstrates the pervasiveness and potential importance of comorbidity between developmental disorders, and results of family, twin, and molecular genetic studies indicate that these comorbidities may be largely explained by shared genetic influences. Additional studies are ongoing to identify the specific genetic polymorphisms that increase risk for each developmental disorder and comorbidity between disorders.

Keywords

Comorbidity; genetics; developmental; ADHD; learning; psychopathology

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Erik.willcutt@colorado.edu.

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Introduction and overview

The past two decades have produced an exponential increase in research examining the genetic and environmental factors that lead to developmental disorders. This rapid accumulation of new knowledge illustrates the potential impact of behavioral and molecular genetic methods to understand the etiology of individual disorders and the frequent co-occurrence of multiple disorders in the same individual. However, results of these studies have also underscored the complex causal pathways that lead to developmental disorders, demonstrating clearly how much is yet to be learned.

The overall goal of the current paper is to provide an overview of current knowledge regarding genetic and environmental influences that lead to comorbidity, the co-occurrence of two or more developmental disorders in the same individual. The first section briefly describes why comorbidity may be important by summarizing the extent and implications of co-occurrence between multiple disorders. The second section then describes how studies of families and twins can be used to determine the extent to which the same genetic or environmental influences contribute to comorbidity. The third section summarizes the results of initial studies that have attempted to identify specific genetic or environmental influences that contribute to cross-disorder genetic risk. The chapter concludes by describing key clinical implications and future directions for this work.

Why is it important to understand comorbidity?

Comorbidity is clearly the rule rather than the exception for virtually all developmental disorders. For example, 60 - 90% of children with attention-deficit/hyperactivity disorder (ADHD), conduct disorder, autism spectrum disorder (ASD), childhood-onset mood disorders, or childhood-onset psychosis also meet criteria for at least one additional disorder (1–6). Further, comorbidity is often associated with greater symptom severity, more extensive and severe functional impairment, less positive response to intervention, and poorer long-term developmental outcomes (6–10).

These results underscore the need to understand the factors that lead to the ubiquitous comorbidity among developmental disorders. Theoretical papers have described over 20 competing models that could account for comorbidity between developmental disorders, including the possibility that shared risk factors may increase risk for multiple disorders (11; 12). The next section summarizes how family and twin studies have been used to test the extent to which shared genetic and environmental risk factors may contribute to comorbidity between developmental disorders.

Behavioral genetic studies

Individuals cannot be randomly assigned to different environmental or genetic backgrounds. Therefore, family and twin studies take advantage of naturally occurring events to estimate the relative influence of genetic and environmental factors on a trait or disorder (for a detailed overview of these methods see 13).

Family Studies

Family studies of developmental disorders.—In a family study individuals with and without a specific disorder are identified; then the rate of the disorder in their biological family members is compared. If the disorder occurs more frequently in the relatives of individuals with the disorder than in relatives of individuals without the disorder, this suggests that familial factors increase risk for the disorder. For example, the biological siblings of a child with autism spectrum disorder (ASD) are approximately 10 times more likely to also meet criteria for ASD than the siblings of a child without ASD (14). Similarly, family studies show elevated family risk for most other developmental disorders, including ADHD, learning disabilities, speech and language disorder, and anxiety and mood disorders (15–17).

Familiality of comorbidity.—If two disorders are each significantly familial when they are studied alone, an extension of the family study design can be used to test whether shared familial risk factors contribute to comorbidity between the disorders. If the same familial influences increase risk for both disorders, the disorders should co-occur in the same families more often than expected by chance. Although few studies of developmental and intellectual disabilities have used this approach, studies have reported shared familial risk factors for several pairs of disorders. For example, family members of children with reading disability (RD) or ADHD are 2–3 times more likely to meet criteria for the other disorder than family members of children without RD or ADHD (16), and similar evidence of shared familial risk factors has been reported for math disability and reading disability (18), and for autism spectrum disorders and both ADHD and anxiety disorders (19).

Limitations of family studies.—Overall, the results of family studies suggest that familial factors shared across disorders may contribute to the frequent comorbidity between developmental disorders, and these shared familial influences may potentially reflect common genetic influences. However, family studies cannot provide conclusive evidence regarding genetic effects because members of biological families living in the same home share both some of their genes and their home environment. Therefore, other methods such as twin studies are needed to determine the relative contributions of genetic and family environmental influences to each individual disorder and any comorbidity between disorders.

Twin studies

By comparing the similarity of pairs of identical versus fraternal twins, twin studies are able to estimate the relative importance of genetic and environmental influences on the development of a disorder. Identical twins are also called monozygotic (MZ) twins because they come from a single egg, and therefore share all of their genetic sequence. In contrast, fraternal (dizygotic, or DZ) twins share half of their genetic sequence in regions of the genome that vary across people, the same as a pair of biological siblings.

The basic twin model provides estimates of three parameters. *Heritability* indicates the extent to which a disorder is due to genetic influences. This is expressed as a proportion or percentage of all causal factors that contribute to a disorder, so a heritability of .50 or 50%

would indicate that genetic risk factors account for half of the risk for the disorder. The remaining variance that is due to environmental factors is subdivided to distinguish two types of environmental influences. *Shared environmental influences* are environmental factors that increase the similarity of individuals within a family in comparison to unrelated individuals in the population. These effects may potentially include environmental influences within the home or any other shared experiences such as mutual friends or shared teachers. In contrast, *nonshared environmental influences* affect only one member of a twin pair or affect the two twins differently, leading to differences between twins in the same family. For example, nonshared environmental risk factors could include a head injury or other accident, a traumatic event, or exposure to physical or sexual abuse (if other family members were not similarly exposed or affected).

Twin studies of developmental disorders.—Twin studies consistently report moderate to high heritability for most developmental disorders. For example, our review of all published studies of learning disabilities and ADHD indicated that heritability is moderate to high for multiple dimensions of learning difficulties (40 - 80%) and for the inattention and hyperactivity-impulsivity symptom dimensions (60 - 80%) that define ADHD (20). Heritability estimates are also significant and large in magnitude for autism spectrum disorders (21), specific language impairment (22), and internalizing and externalizing symptomatology (23;24). In contrast to the strong influence of genes, shared environmental influences play only a small role in most developmental disorders, and the susceptibility that is not explained by genetic influences mostly reflects nonshared environmental factors that are specific to the individual.

Twin studies of comorbidity.—Similar to the logic of family studies of comorbidity, multivariate extensions of the twin study design can be used to test whether comorbidity is due to genetic or environmental influences that are shared across disorders. For example, shared genetic influences account for nearly all of the phenotypic covariance between ADHD and learning disabilities, particularly for symptoms of inattention (25–27). Shared genetic influences also contribute to comorbidity between ADHD and internalizing disorders, externalizing disorders, and autism spectrum disorder (27–29), and a similar pattern emerged in twin studies of comorbidity between other pairs of childhood disorders such as anxiety and depression, and ADHD and conduct disorder (25;27–30).

While more research is needed on many frequent comorbidities, the available literature suggests that comorbidity is often due to shared genetic influences that increase risk for multiple disorders. In contrast, developmental disorders are distinguished by other genetic and environmental risk factors that are unique to each disorder. These promising results led to a new generation of studies that attempted to identify the specific genetic loci underlying these genetic influences.

Molecular genetic studies

Molecular genetic methods can now be used to screen the entire human genome for genes that increase risk for individual developmental disorders or shared risk across disorders. The high heritability of most developmental disorders led to initial optimism that specific genes

would be identified that explained a large proportion of the genetic risk. However, the genetic basis of developmental disorders has turned out to be much more complicated than expected.

Rather than finding specific genes with large effects on each disorder, studies of specific genes and scans of the entire human genome indicate that each genetic risk factor leads to a very small increase in risk (usually far less than 1% of the total risk for the disorder). These findings suggest that developmental disorders are likely to be due to the combined effects of a large number (at least dozens, and potentially hundreds) of genetic and environmental risk factors, each of which leads to a small increase in risk for the disorder in isolation. This pattern has now been reported for ASD, ADHD, reading and math disability, and nearly all other disorders that have been studied in children and adults, including a multisite study of over 150,000 individuals with and without schizophrenia (31–35).

The results of molecular genetic studies also have important implications for comorbidity. If a large number of genes act together to cause each individual disorder, it is plausible that a subset of these genes are likely to be shared risk factors that contribute to the frequent comorbidity among developmental disorders, whereas others may be uniquely associated with each disorder. A handful of initial studies have tested directly whether specific genetic loci contribute to comorbidity between developmental disorders. For example, initial studies identified potential genetic loci with effects on both RD and ADHD on chromosome 6 (36) and chromosome 15 (37;38). However, these results have replicated inconsistently, and it is likely that these and other studies are underpowered due to the small effect sizes for individual loci.

In addition to studies of single genetic loci, results of genome-wide analyses can also be used to test for shared genetic influences on multiple disorders across the entire genome. Even if the effect of each individual gene is quite small, this approach provides an estimate of the extent to which the combined effects of all genetic risk factors contribute to comorbidity between disorders. Only a handful of studies have applied this novel approach exclusively to samples of developmental disorders during childhood, initial results suggest that shared genetic influences account for much of the comorbidity between adult disorders that frequently have a childhood onset, such as ASD, ADHD, schizophrenia, depression, and bipolar disorder (39).

Conclusions and Future directions

In summary, several decades of research have underscored the pervasiveness and potential importance of comorbidity among developmental disorders, and results of family, twin, and molecular genetic studies indicate that these comorbidities may be largely explained by shared genetic influences. However, the genetic etiologies of developmental disorders are complex, with a large number of genetic risk factors acting in combination with a range of environmental risk factors to lead to the development of each individual developmental disorder and the frequent comorbidity between disorders. This final section examines the broader implications of these results and suggests several important next steps for behavioral and molecular genetic studies of developmental disorders and their comorbidity.

Strategies to increase the utility and predictive power of genetic studies

Multisite consortia.—Results of behavioral and molecular genetics studies suggest that causal pathways for developmental disabilities are substantially more complex than the field realized even a decade ago. Because the effect of each specific genetic risk factor is likely to be very small, future studies will require extremely large samples that are simply not feasible for a single laboratory to collect in isolation. Fortunately, innovative statistical techniques have been developed to combine information from different studies, allowing networks of investigators to work together to build upon the initial progress of individual laboratories.

One of the largest collaborative networks to date is the Psychiatric Genetics Consortium (PGC), an international collaboration that initially combined data from studies of ASD, ADHD, bipolar disorder, depression, and schizophrenia (39). The PGC has now expanded to include large studies of eating disorders, substance use disorders, and post-traumatic stress disorder (PTSD), and additional specific consortia have been established for developmental disorders such as ASD (40), ADHD (41), and language disorders (<http://genlang.org>). Future extensions and expansions of these types of collaborative networks are likely to continue to accelerate progress in the field.

Gene systems and polygenic risk scores.—Rather than testing the effect of a single genetic polymorphism, another innovative approach is to analyze systems of multiple related genes identified because they play a role in a biological pathway that is implicated in the disorder (such as the dopamine system for ADHD or the serotonin system for depressive disorders).

Another approach creates polygenic risk scores that reflect the summation of all of the positive effects identified in a genome-wide screen. A polygenic risk score derived in one sample is then validated by testing if the score significantly predicts individual disorders or their comorbidity in an independent sample. For example, a polygenic risk score derived from the overall PGC predicted symptoms of ASD (40) and ADHD (42) in other samples, and these results have added to the literature suggesting that genetic effects may be especially strong in the subset of children with comorbid ADHD and conduct disorder (43). However, relatively few studies of developmental disorders have used this approach and initial effect sizes still remain small, reflecting the limits of the current explanatory power of this method.

Gene X environment interactions.—Rather than focusing exclusively on genetic or environmental risk factors alone, studies have begun to include genetic polymorphisms and environmental measures in the same analyses to test for gene x environment (G x E) interactions. G X E interactions occur if the expression of a gene varies as a function of the specific environment. For example, diathesis-stress interactions occur when the co-occurrence of a genetic vulnerability (the diathesis) and an environmental risk factor results in more severe symptomatology than would be expected based on their additive combination.

Several interesting G X E interactions have been reported in the literature, including a diathesis-stress interaction between the serotonin transporter gene and environmental stress

that may contribute to depression (44) and an interaction between dopamine system genes and prenatal exposure to nicotine or alcohol that may increase risk for ADHD (reviewed in 45). However, these and several other initial positive G X E interactions have replicated inconsistently, suggesting that reports of significant G X E interactions should be interpreted cautiously (46).

Clinical Implications and future collaborative research

There is currently no valid genetic test for any individual developmental disorder or for comorbidity between disorders, and it appears to be unlikely that a definitive diagnostic test will be developed in the near future. Because developmental disorders have complex, multifactorial etiologies in which each risk factor confers only a small increase in susceptibility, it is unlikely that any specific risk factor will have sufficient predictive power to be useful as a diagnostic measure.

Having said that, it may eventually be possible to develop probabilistic risk profiles that combine information from all genetic risk factors to provide a measure of overall genetic risk. These risk profiles could be used to identify individuals who are at higher risk for a specific developmental disorder or for multiple comorbid disorders, facilitating primary prevention or early intervention to reduce the probability that the child will eventually develop one or more disorders.

Further, even if behavioral and molecular genetic studies do not identify a definitive genetic test for ADHD or other developmental disorders, these methods may still have important clinical implications in the future. For example, the consistent finding that the same genetic risk factors increase risk for multiple disorders suggests that similar treatments may be effective for multiple disorders, and underscores the need to screen systematically for all relevant disorders as part of a comprehensive clinical assessment.

Finally, it is worth noting that procedures for DNA collection and genetic analysis continue to become more automated and efficient. It is rapidly becoming possible for researchers with relatively modest budgets and minimal specific training in behavioral or molecular genetics to collaborate with experts in DNA analysis to incorporate genetically informative methods as one part of their study.

In the future, the capacity to easily apply these methods more broadly is likely to facilitate an extraordinary kind of collaborative synergy between behavioral and molecular genetic researchers and investigators focusing on other aspects of developmental disorders, strengthening research across all levels of analysis. Studies that integrate these approaches are likely to improve models of the pathophysiology of developmental disorders, and may eventually inform the development of tertiary pharmacological or psychosocial treatments that directly target the physiological and psychological mechanisms that are compromised in each specific developmental disorder, including any shared risk factors that lead to comorbidity between disorders.

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Conflict of Interest

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