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Behavior genetics: Past, present, future

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Abstract

The disciplines of developmental psychopathology and behavior genetics are concerned with many of the same questions about the etiology and course of normal and abnormal behavior and about the factors that promote typical development despite the presence of risk. The goal of this paper is to summarize how research in behavior genetics has shed light on questions that are central to developmental psychopathology. We briefly review the origins of behavior genetics, summarize the findings that have been gleaned from several decades of quantitative and molecular genetics research, and describe future directions for research that will delineate gene function as well as pathways from genes to brain to behavior. The importance of environmental contributions, at both genetic and epigenetic levels, will be discussed. We conclude that behavior genetics has made significant contributions to developmental psychopathology by documenting the interplay among risk and protective factors at multiple levels of the organism, by clarifying the causal status of risk exposures, and by identifying factors that account for change and stability in psychopathology. As the tools to identify gene function become increasingly sophisticated, and as behavioral geneticists become increasingly interdisciplinary in their scope, the field is poised to make ever greater contributions to our understanding of typical and atypical development.

Since Gregor Mendel's experiments with pea plants in the mid-1860s that led to the foundation of modern genetics, scientists have strived to uncover the genetic basis of health, behavior, and abilities. In the social and clinical sciences, nature and nurture have been framed in adversarial terms, with the focus of research swinging back and forth from environmental to biological determinants of the etiology and course of psychopathology. More recently, behavioral geneticists, neuroscientists, and cellular and molecular biologists have abandoned the nature–nurture dichotomy in order to identify various forms of gene–environment interplay. The goal of the current paper is to provide a brief background on the history of behavior genetics research, to summarize some conclusions that can be drawn about the development of psychopathology from the past 40 to 50 years of behavior genetics research, and to describe promising directions in which the field is headed.

As a discipline, developmental psychopathology shares a number of premises with behavioral genetics. First, both disciplines are premised on the assumption that information about normal development can be gleaned from the study of psychopathology and that information about psychopathological developmental can be gleaned from the study of normative behavior and abilities (Cicchetti, 1984). Second, both disciplines are concerned with how normal and abnormal behavior, health, cognitive abilities, and personality characteristics are multiply determined by the interplay among individual-level (e.g., genetics, physiology), family-level, and extrafamilial influences (Cicchetti, 1993), although developmental psychopathologists emphasize cultural influences on development more than behavioral geneticists typically do. Just as one of the goals of developmental psychopathology is to understand the etiology and course of psychopathology (Sroufe & Rutter, 1984), many behavioral geneticists are concerned with identifying factors that contribute to individual change and stability. Thus, the findings from the past 40 to 50 years of research in behavior genetics should be relevant to researchers in developmental psychopathology.

Some definition of terms will facilitate the discussion that follows. *Behavior genetics* consists of quantitative genetics (also known as biometrical genetics) and molecular genetics. *Quantitative genetics* is the statistical partitioning of genetic and environmental influences on variation in a phenotype (i.e., a trait or characteristic of an individual). For example, quantitative geneticists might be interested in how much latent genetic versus environmental factors account for individual differences in symptoms of psychopathology or in liability to psychiatric disorder. *Heritability* describes how much of the phenotypic variation in a population at a particular point in time can be accounted for by genetic variation in the population (Plomin, DeFries, McClearn, & McGuffin, 2008). *Molecular genetics* involves the search for genes that influence traits and disorders and research to identify gene function. For example, molecular geneticists might be interested in whether they can identify specific gene variants that increase risk for psychiatric disorder and in how those

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genes function to produce proteins or regulate gene expression.

A Brief History of Quantitative Genetics

Familial resemblances in human traits have been remarked on since antiquity (Aristotle, trans. 1942), and have been the subject of scientific study for 150 years (Galton, 1869). The mathematical foundations of quantitative genetics were provided by R. A. Fisher (1918) and Sewall Wright (1921), who extended Mendel's single-gene model to include the influence of multiple genes on a phenotype. Prior to the 1960s, quantitative genetics was mainly informed by observations from animal husbandry and agronomy. The resulting selection and inbred strain studies demonstrated empirically that most complex behaviors and abilities resulted from the influence of multiple rather than single genes (Plomin et al., 2008). In recent decades researchers have accumulated a vast catalog of data from family samples to quantify genetic and environmental influences on complex human traits. Twinning and adoption give rise to natural experiments in which the effects of the familial environment and genetic inheritance, confounded in other pedigrees, can be distinguished. We describe each of these designs in turn.

Twin and adoption designs

Twin studies. The twin study is premised on the observation that monozygotic (MZ; i.e., identical) twins share 100% of their segregating genes, whereas dizygotic (DZ; i.e., fraternal) twins share an average of 50% of their segregating genes. Quantitative genetic models decompose phenotypic variation in a population into genetic and environmental components. Shared (or common) environments are those that make children growing up in the same family similar to one another, and nonshared (or unique) environments make children growing up in the same family different from one another. Assuming that the environments inhabited by MZ twins do not make them more phenotypically similar than do the environments inhabited by DZ twins (known as the trait-specific equal environments assumption), the only thing that can increase the similarity of MZ relative to DZ twins is their greater genetic similarity. Conversely, if MZ and DZ twins are equally similar to one another, then the environments they inhabit (i.e., shared environments) must increase within-pair similarity. Finally, nonshared environments (or measurement error) must cause MZ twins to be different from each other. The classical twin model can be supplemented with data from other relatives to test a wider range of hypotheses, including the influences of cultural transmission, genetic nonadditivity, and the processes that give rise to nonrandom mating. For an excellent introduction to the logic of the twin design, see publications by Plomin et al. (2008) and Rijsdijk and Sham (2002).

The twin design has several limitations. First, the equal environments assumption is apparently frequently violated. MZ twins have more similar experiences than do DZ twins (Kendler & Baker, 2007) and MZ twins share a more similar prenatal environment than do DZ twins (Machin & Keith, 1999). However, it is not true that a more similar experience of the world makes MZ twins more alike than are DZ twins in terms of personality (Borkenau, Riemann, Angleitner, & Spinath, 2002) or emotional and behavioral problems (Cronk et al., 2002). In the case of the prenatal environment, approximately 75% of MZ twins are monochorionic, meaning they share both the placenta and the chorion, which is the outer membrane of the amniotic sac (Shulman & Cohen, 2006). In contrast, DZ twins are rarely monochorionic (Shulman & Cohen, 2006). Monochorionicity can result in increased competition for intrauterine resources (as seen in twin to twin transfusion syndrome; Harkness & Crombleholme, 2005; Lewi, Debrest, Dennes, & Fisk, 2006). Consequently, MZ twins who share a chorion are less correlated for birth weight than are twins who do not share a chorion (Victoria, Mora, & Arias, 2001; Vlietinck et al., 1989). Thus, whether the equal environments assumption is violated and how much those violations bias heritability estimates may depend on the phenotype in question.

More recently, basic assumptions of the twin design have been challenged by data suggesting that MZ twins are not genetically identical and that DZ twins may share less than 50% of their segregating genes on average, because of the possibility that DNA structure can change across the life course (Charney, 2012). These findings challenge the logic of the twin design by suggesting that phenotypic differences within MZ twin pairs are not solely attributable to nonshared experiences. For example, de novo mutations and copy number variants (CNVs; Veltman & Brunner, 2012) can give rise to phenotypes of interest to developmental psychopathologists, such as autism (Levy et al., 2011), schizophrenia (Xu et al., 2012), and mental retardation (Vissers et al., 2010). The small-scale studies conducted to date suggest that discordance for structural variants in MZ pairs is likely to be rare, tissue specific, and unrelated to phenotype (Ehli et al., 2012). Genomewide resequencing projects have not found replicable intrapair differences (Baranzini et al., 2010; Veenma et al., 2012). Meanwhile, the assumption that DZ twins share 50% of their segregating genotypes has been empirically validated in a sample of more than 10,000 pairs who were typed using a genomewide panel of markers (Wray, Goddard, & Visscher, 2007). On average, the siblings shared 50% of their genome identity by descent (IBD), with 95% of the sample sharing between 42% and 58% IBD.

Finally, it bears noting that for some phenotypes at least, heritability estimates are fairly robust to different methods of estimation. Some biometric approaches are not premised on the assumption that MZ twins share 100% of their genes, whereas DZ twins share an average of 50% of their segregating genetic material. These biometric approaches produce heritability estimates for height (Visscher et al., 2006; Yang et al., 2010), unipolar depression (Lubke et al., 2012), bipolar disorder (Lee, Wray, Goddard, & Visscher, 2011), and cognitive ability (Davies et al., 2011) that are similar to heritabil-

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ity estimates derived from twin and adoption studies. However, it must be noted that for other phenotypes (e.g., smoking behavior, personality dimensions), heritability estimates derived from twin and adoption studies versus "assumption-free" approaches differ more substantially (Lubke et al., 2012; Vinkhuyzen et al., 2012).

Adoption studies. Genetic and environmental influences on complex traits are estimated in the adoption design by comparing adoptive siblings (who are genetically unrelated) and nonadoptive siblings (who share an average of 50% of their segregating genes). The adoption design is also used to identify genotype–environment correlations and Genotype × Environment (G × E) interactions, as will be discussed in greater detail in the following section. Like twin studies, adoption studies are characterized by various limitations. First, because adoptive families are closely screened by child welfare services, they tend to be less disadvantaged and less dysfunctional compared with nonadoptive families (McGue et al., 2007; Stoolmiller, 1999). Thus, the adoption design can be relatively uninformative about the effects of extreme adversity, and the restricted range of environments in adoptive families can bias estimates of genetic and environmental influences (Stoolmiller, 1999), although it has been demonstrated that range restriction does not affect the magnitude of adoptive sibling correlations for disinhibitory behaviors and IQ (McGue et al., 2007). Second, the adoption design presumes that adoptive children do not maintain contact with their biological parents. Historically, this assumption has probably been valid, as many samples of adoptees were recruited at a time when both closed and international adoptions were common. However, as open adoptions have become increasingly common, researchers must monitor and quantify the amount of contact between adoptees and biological parents in order to determine whether and how much contact biases heritability estimates (Leve et al., 2007).

In summary, quantitative geneticists are concerned with quantifying how much of the variation in a phenotype can be accounted for by latent genetic and environmental factors. The twin and adoption designs produce these estimates by testing whether sibling similarity for a trait varies as a function of sibling genetic relatedness. Although the fundamental premises on which quantitative genetic designs are based have been challenged, heritability estimates are likely to be fairly robust to these violations.

What twin and adoption studies have taught us about the development of psychopathology: Virtually all complex human traits are heritable and genetic influences are largely stable over time

Developmental psychopathology and quantitative genetics are both premised on the assumption that phenotypes are multiply determined by individual and environmental factors. Findings from twin and adoption studies have highlighted the importance of two types of influence in particular. First, as noted by Turkheimer (2000, p. 160) in a paper entitled "Three Laws of Behavior Genetics and What They Mean," "All human behavioral traits are heritable." Twin and adoption studies have played a key role in demonstrating the pervasiveness of genetic influences on variation in behavior and traits, thus challenging the conventional wisdom that variation in children's environments determined individual differences in their behavior.

Does a child's environment have no bearing on his or her development? Quantitative genetic studies also address this question. Because genetic factors tend to account for about 50% of phenotypic variation, it must also be true that human behavioral traits are under environmental influence. It is counterintuitive that the environments that account for substantial variation in a phenotype are not typically those that are shared by children growing up in the same family but, rather, nonshared environments that make children growing up in the same family different from one another (Plomin & Daniels, 1987; Reiss, Neiderhiser, Hetherington, & Plomin, 2000; Turkheimer & Waldron, 2000).

Second, twin and adoption studies have also highlighted the importance of genetic and nonshared environmental factors in accounting for phenotypic change and stability (Ronald, 2011). For example, longitudinal studies have demonstrated that symptoms of attention-deficit/hyperactivity disorder (ADHD) are moderately stable over time (Biederman et al., 1996). Quantitative genetic studies of ADHD have shown that symptom stability is largely accounted for by the same genes operating over time, whereas change in symptomatology is accounted for by new genetic influences and by unique environmental influences that tend to operate at one point in time but not at the next (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005; Price et al., 2005; Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004).

In another effort to model genetic and environmental influences on phenotypic change and stability, behavioral geneticists have integrated general growth mixture models into a biometrical modeling framework (Larsson, Dilshad, Lichtenstein, & Barker, 2011). For example, Fontaine, Rijsdijk, McCrory, and Viding (2010) estimated trajectories of callous–unemotional traits across three time points (ages 7, 9, and 12 years) in a sample of twins. They identified four trajectory groups (stable low, stable high, increasing, and decreasing), with the stable high group also showing the highest levels of conduct problems and hyperactivity. For boys, approximately 60% to 80% of the liability for group membership was largely accounted for by genetic factors, with the rest accounted for by nonshared environmental factors. Genetic influences on membership in the stable high group were greater than genetic influences on membership in the other trajectory groups. In contrast, genetic influences on trajectory membership were relatively weaker and shared environmental influences were relatively stronger for girls. Such approaches have the potential to identify whether genetic and environmental factors differentially account for patterns of change and stability in behavior or symptomatology.

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Gene–environment interplay is pervasive

At the same time that quantitative geneticists have demonstrated conclusively the genetic underpinnings of virtually all complex human behaviors, they have also demonstrated that the nature–nurture dichotomy is false. Over the past 15 years, researchers have become increasingly interested in demonstrating how genes and environments work together to produce phenotypic variation. Gene–environment interplay refers to three processes, two of which will be described in this section (Kendler & Eaves, 1986; Plomin, DeFries, & Loehlin, 1977; Rutter & Silberg, 2002). First, genotype–environmental correlations refer to genetically based individual differences in exposure to environments. Second, G × E interactions refer to genetically based individual differences in susceptibility to environments. Social regulation of epigenetic and gene expression profiles will be described in the section on molecular genetic approaches.

Gene–environment interactions. In developmental psychopathology research more broadly, researchers have been interested in the extent to which environmental factors moderate the magnitude of associations between individual-level predictors and outcomes. Thus, being impulsive is highly predictive of delinquent behavior in socially disadvantaged neighborhoods, but it is a weaker predictor of delinquency in more affluent neighborhoods, where there may be more family and community constraints on behavior (Lynam et al., 2000).

In the context of quantitative genetic studies, G × E interactions highlight the degree to which the influence of individual-level characteristics (e.g., genotype) are either enhanced or constrained depending on the environment. For example, studies of alcohol and tobacco use show that genetic factors account for relatively more of the variation in these phenotypes under conditions that facilitate substance use, when, for instance, there are low taxes on substances (Boardman, 2009), alcohol is readily available (Boardman, 2009; Kendler, Gardner, & Dick, 2011), social norms exist to encourage drinking (Boardman, Saint Onge, Haberstick, Timberlake, & Hewitt, 2008; Timberlake et al., 2007), youth affiliate with deviant peer groups (Kendler et al., 2011), youth live in an urban versus a rural environment (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001), families do not participate in organized religion (Timberlake et al., 2006), and parents engage in low levels of monitoring (Dick et al., 2007). Similarly, genetic influences on adolescent externalizing problems (including antisocial behavior and substance use) are increased in the context of a broad range of adversities, all of which could either promote or facilitate opportunities to engage in externalizing behaviors (Hicks, South, DiRago, Iacono, & McGue, 2009).

Gene–environment correlations. Developmental psychopathologists have long been interested in correlations between persons and environments. Person–environment correlations are hypothesized to drive developmental processes, including personality development (Caspi & Moffitt, 1995) and the development of psychopathology (Dohrenwend et al., 1992). Person–environment correlations may also confound observed associations between risk exposures and outcomes in which, for example, becoming a teen mother may simply be a marker for individual characteristics that predate the transition to motherhood (e.g., impulsivity, low IQ) and that explain subsequent life course outcomes rather than a causal risk factor per se (Jaffee, 2002).

Gene–environment correlations can be thought of as special cases of person–environment correlations. Gene–environment correlations take several forms (Kendler & Eaves, 1986; Plomin et al., 1977). Passive gene–environment correlations occur when genes common to parents and children account for observed associations between children's rearing environment and their behavior or abilities. Evocative gene–environment correlations occur when a child's genotype (via the child's behavior, abilities, or other characteristics) evokes a response from his or her environment. For example, children who are genetically predisposed to engage in oppositional and aggressive behavior may provoke their parents to use physically punitive forms of discipline (Jaffee et al., 2004). Active gene–environment correlations occur when individuals select or "niche-pick" environments based on their genetic proclivities. For example, a child with perfect pitch may be more likely to lobby her parents for music lessons than will a child who is less musically inclined.

Like person–environment correlations, gene–environment correlations potentially confound causal accounts of the relationships between risk factors and outcomes. For example, the fact that parents provide a child's genotype as well as a child's rearing environment means that correlations between parent and offspring behavior are not unambiguously interpretable. Although a parent's use of harsh physical discipline could cause a child to become aggressive, it is equally possible that this association could be explained by shared genes that predispose both parents and children to aggressive behavior (DiLalla & Gottesman, 1991; Jaffee, Caspi, Moffitt, & Taylor, 2004).

Like person–environment correlations, gene–environment correlations are also hypothesized to underlie developmental processes. In a simulation study, Beam and Turkheimer (2013) showed that the apparent increase in the heritability of many human traits (e.g., intelligence, personality traits) can be explained by gene–environment correlations that lead to increasing differentiation of DZ twins relative to MZ twins. Thus, small, genetically based individual differences in behavior and abilities become amplified over time as individuals expose themselves to experiences for which they have some affinity and those experiences in turn reinforce and widen preexisting individual differences. Failing to model gene–environment correlations leads to an apparent increase over time in the heritability of a phenotype when, in fact, genetic influences on the phenotype remain stable over time.

Hicks et al. (2013) provide an empirical example of how gene–environment correlations underlie the process by which

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personality can be amplified into psychopathology (Caspi & Moffitt, 1995). In their sample of 11-year-old twins, Hicks et al. (2013) measured the tendency to follow rules and endorse conventional norms, a construct they named "socialization" that shares many features with the Big 5 factor of conscientiousness (Costa & McCrae, 1992). Youth with lower scores on the measure of socialization subsequently experienced higher levels of contextual risk in midadolescence, such as a deviant peer group or a conflictual relationship with parents. The relationship between socialization and contextual risk was largely accounted for by genetic and shared environmental factors common to both constructs, indicative of an active gene–environment correlation. Moreover, youth with lower scores on the socialization measure in early adolescence tended to engage in higher levels of substance use in late adolescence, an association that was mediated by their exposure to contextual risk factors. Thus, genetically based individual differences in personality increased the likelihood that some youth would be exposed to higher levels of contextual risk than would others, with implications for the emergence of substance-use problems in late adolescence.

Factors That Account for Variation in the Normal Range Are Frequently Similar to Factors That Account for Variation at the Extremes

A central premise of developmental psychopathology is that the study of normative development is informative about nonnormative development, with the reverse being equally true (Cicchetti, 1984). This perspective presumes that psychopathology reflects the quantitative extreme of some underlying distribution rather than a pattern of behavior or cognitions characterized by a qualitatively distinct etiology. For example, the ability to understand other people's beliefs, desires, and intentions (i.e., theory of mind) develops around the age of 4 or 5 years (Wellman, Cross, & Watson, 2001). Delayed and atypical development of this understanding is a hallmark of autism spectrum disorder (Happé, 1995; Leslie & Thaiss, 1992) and illustrates the extent to which a theory of mind facilitates social communication and interaction.

Like developmental psychopathology researchers, behavioral geneticists are interested in connections between normal variation and variation at the phenotypic extremes. In the case of autistic traits, it has been shown that the heritability of autistic traits at the extremes of the distribution is similar to the heritability of autistic traits in the normal range of the distribution, suggesting that these traits lie along a continuum rather than represent categorically distinct entities (Robinson et al., 2011; Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006; Lundstrom et al., 2012). A similar pattern of findings has been observed for ADHD (Lundstrom et al., 2012) and learning disabilities (Bishop, 2009; Plomin & Kovas, 2005). In some cases, however, the etiology of variation at the extremes of a distribution appears to vary substantially from the normal range, as in the case of callous–unemotional traits (Viding, Jones, Frick, Moffitt, & Plomin, 2008). Moreover, disorders are likely to be heterogeneous in origin, with many cases arising from genes of small effect that cumulatively cross a threshold from normal to abnormal, but others caused by rare mutations that are not expected to account for variation in the normal range (Bishop, 2009).

Molecular Genetic Approaches

Whereas quantitative genetics is concerned with identifying how much of the variation in complex human traits is accounted for by genetic versus environmental factors, molecular geneticists are concerned with identifying specific genes that give rise to psychiatric disorder and in the interplay of genes and environments. Thus, molecular genetics, like quantitative genetics, shares with developmental psychopathology an interest in how factors at multiple levels of the organism shape trajectories of adaptive and maladaptive functioning.

As in the previous section, our focus is on behavioral genetic approaches in human samples. Thus, we do not discuss experiments to identify gene function that are available only in animal studies, including approaches that manipulate the expression level of a target gene (to eliminate expression or overexpress the target protein), using techniques such as site-specific delivery of viral constructs, or through the use of genetic manipulations (Morozov, 2008; Müller, 1999).

The human genome contains approximately 30,000 protein-coding genes (Pennisi, 2003), the majority of which do not vary in the population and many of which are shared with nonhuman primates and rodents (http://www.ornl.gov/sci/techresources/Human_Genome/faq/compgen.shtml). Less than 1% of the human genome varies (meaning that alternate forms of these genes exist) in the population. These variant forms are known as alleles or polymorphisms and molecular geneticists are concerned with testing whether these forms of genetic variation are associated with individual differences in symptomatology or disorder.

Approximately 90% of gene variants are single nucleotide polymorphisms (SNPs), which refer to single base pair differences in a DNA sequence on a gene. There are approximately 3 million SNPs across the human genome. Historically, molecular geneticists have been most interested in "functional SNPs" that fall in coding regions of the gene, where the single base pair change alters the protein product of the gene. Gene variants also include variable number tandem repeats (VNTRs), which refer to regions of the genome where a short nucleotide sequence repeats itself. For example, the monoamine oxidase A (*MAOA*) gene is a VNTR that comprises a 30 base pair sequence that repeats itself anywhere from two to five times. In the case of this *MAOA* VNTR, the number of repetitions is associated with the transcriptional efficacy of the gene (Sabol, Hu, & Hamer, 1998). Finally, CNVs refer to large regions of the genome where a nucleotide sequence is duplicated or deleted, potentially altering gene regulation in the region of the CNV and resulting in disease (Feuk, Carson, & Scherer, 2006). Although some CNVs are inherited, others

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are de novo mutations, arising spontaneously during meiosis (Stankiewicz & Lupski, 2010). Other structural variants exist that are beyond the scope of this discussion.

Molecular genetic methods

Linkage studies identify genomic regions containing risk variants by matching the patterns of IBD between related individuals with their concordance for disease. The principle is that any two relatives who both suffer a heritable disease will tend to have inherited the same susceptibility loci. This approach is particularly powerful for detecting rare and highly penetrant loci (i.e., those for which carriers have a high risk of disease). Thousands of monogenic disorders have been mapped in this way, often using extended pedigrees. A more common research design for complex traits employs sibling pairs. The advantages of linkage studies are that results can be found using samples of hundreds (rather than thousands) of subjects and that genomewide scans can be conducted using panels of hundreds (rather than hundreds of thousands) of genetic markers. The corresponding disadvantages are that linkage analysis lacks power to detect the common loci with small effects that account for the majority of heritable trait variance. Moreover, linkage analysis identifies only a broad genomic region that may span dozens of genes and include many thousands of polymorphisms. Consequently, its usefulness in the mapping of complex traits has extended mainly to the identification of "positional" candidate genes located under replicated linkage peaks, a strategy that has scored such notable successes as the identification of the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) risk locus for Crohn disease (Hugot et al., 2001; Ogura et al., 2001).

Gene association studies identify candidate genes that are hypothesized to increase risk for psychopathology. Candidate genes are those about which researchers hold some a priori hypothesis. For example, there is a long history of addiction researchers studying gene variants involved in dopamine neurotransmission because of the role dopamine plays in reward (Berridge, 2007; Wise, 2004). Gene association studies test whether specific gene variants predict case versus control status or variation in psychiatric symptoms.

Gene association studies have been criticized for two reasons. First, there have been very few replications in research on psychopathology, suggesting that many novel findings were false positives. Second, relatively few significant associations have been identified in protein-coding regions of the genome, suggesting that researchers do not know enough about the neurobiological basis of the phenotypes they study to construct plausible genetic hypotheses (Duncan & Keller, 2011).

Genomewide association studies (GWAS) were meant to be a hypothesis-free corrective to the shortcomings of candidate gene association studies. In GWAS, hundreds of thousands of common SNPs (i.e., minor allele frequencies exceed 1%) are "tagged" across the genome (i.e., they are genotyped on DNA microarray chips) and statistical analyses that make stringent corrections for multiple testing are used to determine whether any of these tagged SNPs are associated with disorder or account for significant variation in symptomatology. SNPs that meet stringent criteria for genomewide significance (typically $p < 10^{-8}$) are considered to be markers for the true causal variants with which they are correlated (i.e., in linkage disequilibrium; Donnelly, 2008). In theory, researchers can follow up on genomewide "hits" by fine-mapping the region around the hit and, if potentially causal variants are identified, they can use functional assays to determine which variant causes disease (Donnelly, 2008). In practice, this process has proved to be challenging, and even when GWA studies have produced strong evidence of association for specific SNPs, functional follow-ups have generally not located the causal variants (Williams et al., 2011).

DNA sequencing. Sequencing is a method of genotyping the entire nucleotide sequence of a region of a gene, a gene itself, or the entire genome. Exome sequencing describes the process of sequencing only the protein-coding regions of the genome. Whereas gene association studies mainly identify SNPs that are common in the population, sequencing studies capture all forms of genetic variation (e.g., structural variants as well as SNPs), including rare variants. Sequence variation is compared in cases and controls to determine whether rare variants are present in the former versus the latter. In some cases, family trios (e.g., parents and children) are sequenced to determine if the structural variants associated with disorder are *de novo* mutations (Malhotra et al., 2011).

What molecular genetic studies have taught us about the development of psychopathology: Common and rare variants are likely to be implicated in disease risk

Broadly speaking, psychiatric geneticists fall into two camps. Some hypothesize that most common disorders are caused by gene variants that are common in the population (meaning that minor allele frequencies are at least 1%). This is known as the common disease–common variants hypothesis (Lander, 1996; Pritchard & Cox, 2002) and it posits that most diseases are caused by a very large number of common variants, each of which has a very small additive effect on risk for disorder, potentially via their influence on gene regulation rather than protein coding (Donnelly, 2008). Others have hypothesized that common disorders are caused by gene variants that are recently derived and rare in the population but have moderately high penetrance, meaning that possession of the risk allele is strongly associated with expression of the disease (Cirulli & Goldstein, 2010). Associations between rare variants and disorder may reflect equifinality, wherein a set of rare variants increases risk for disorder in one subset of the population and a different set of rare variants increases risk for ostensibly the same disorder in a different subset of the population (Gibson, 2012).

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To date, neither theory nor data decisively favor one hypothesis over the other (Gibson, 2012). GWA studies have identified scores of variants for complex diseases (see the National Human Genome Research Institute catalogue of published GWA studies at http://www.genome.gov/gwastudies), and although there are relatively few instances where genomewide hits for psychopathology have been followed by functional work to identify causal variants, it is more likely that the true casual variants are common rather than rare alleles (Wray, Purcell, & Visscher, 2011). In contrast, the rare alleles hypothesis is more consistent with evolutionary theory; variants that reduce evolutionary fitness should be winnowed from the population. Moreover, with respect to psychiatric phenotypes, rare variants have been implicated in schizophrenia (Stefansson et al., 2008; for reviews, see Mulle, 2012; Rucker & McGuffin, 2012), autism (for reviews, see Betancur, 2011; State & Levitt, 2011), and bipolar disorder (for a review, see Malhotra & Sebat, 2012) with effect sizes that greatly exceed those for common variants identified in GWAS. Even when the additive effects of multiple variants are considered, not just those that exceed genomewide significance levels (Davies et al., 2011; Lee et al., 2011; Yang et al., 2010), the variance in the phenotype that is explained by genetic variance often fails to match heritability estimates, leading to questions about "missing" heritability (Manolio et al., 2009). The common versus rare variants debate is unlikely to resolve in an either/or understanding of disease risk; both common and rare variants are likely to be implicated in disease. Establishing the contributions of common and rare variants will require functional approaches that delineate the mechanisms by which these variants increase risk for disorder against a given genetic backdrop.

Genotype moderates the effect of experiences and exposures on risk for psychopathology and the course of psychopathology

The possibility that individual differences in genotype explain why some individuals succumb to risk whereas others maintain positive functioning in the face of adversity is a potential explanation for multifinality in development: the notion that exposure to a given risk factor can result in many different outcomes (Cicchetti & Rogosch, 1996). G × E interactions predict that specific alleles will at least partly determine whether or not a particular risk exposure will result in the manifestation of psychopathology.

Although gene–environment interplay is likely to involve *biological* interactions, wherein one or more genes and one or more environments increase risk for disease because they are involved in the same causal pathway in an individual (Rothman, Greenland, & Lash, 2008), behavioral geneticists have mainly concerned themselves with the search for *statistical* interactions, albeit with biologically plausible underpinnings. Statistical interactions do not allow for any inferences about the biological mode of action. They simply establish whether the effect size of an exposure on risk for disease changes across different levels of the genotype, measured in a particular scale (e.g., an additive vs. a dominant scale).

Although quantitative genetic studies published in the 1990s established that genetic influences on a phenotype were stronger under some conditions versus others (as reviewed earlier), the first demonstration of a measured G × E interaction in the psychopathology literature appeared in 2002. This study found that men who carried the low-activity variant of a 30 base pair VNTR in the *MAOA* gene and who had experienced maltreatment in childhood engaged in significantly higher levels of antisocial behavior in childhood and adulthood compared with those who carried the low-activity variant but had not been maltreated. In contrast, among men who carried the high-activity variant of the *MAOA* gene, a childhood history of maltreatment was not predictive of their antisocial behavior in either childhood or adulthood (Caspi et al., 2002). Since the publication of this and a subsequent paper by the same group (Caspi et al., 2003), the literature on G × E interactions has grown exponentially (Aschard et al., 2012).

Studies of G × E interaction not only provide examples of multifinality in development, they also demonstrate how gene–environment interplay influences the course of psychopathology. For example, in a sample of young adults, childhood maltreatment predicted persistent depression, but not intermittent depression, among individuals who carried the short allele of the serotonin transporter promoter gene-linked polymorphism. In contrast, childhood maltreatment was unrelated to either persistent or intermittent depressive disorder among individuals who were homozygous for the long allele (Uher et al., 2011). Another study found that the genotype encoding for cholinergic receptor muscarinic 2, *CHRM2*, differentiated youths who were on a high and stable trajectory of externalizing problems from those who were on a low and decreasing trajectory, particularly if youth affiliated with a deviant peer group (Latendresse et al., 2011).

The statistical interactions identified in G × E studies are consistent with both data and theory. For example, heterogeneity in response to exposures or experiences is the rule rather than the exception in epidemiological studies. Moreover, the consistently small genetic effects identified in gene association studies could be produced if there was significant heterogeneity across a sample in the magnitude of genetic effects arising from differential exposures (Moffitt, Caspi, & Rutter, 2005). From an evolutionary standpoint, individual differences in susceptibility to rearing environments would provide a hedge against uncertainty about the future. Whereas high responsivity to the environment would confer reproductive advantages when rearing environments were good predictors of future conditions, low responsivity would confer reproductive advantages when rearing environments had poor predictive power (Belsky & Pluess, 2009).

Nevertheless, there have been cogent criticisms of the literature identifying G × E interactions (Duncan & Keller, 2011). Criticisms of this literature fall into four related categories. The first is that positive findings are disproportion-

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ately represented in peer-reviewed journals, although it is doubtful that publication bias is any less common in other areas of the social and natural sciences. The second criticism is that most G × E studies are underpowered to detect interaction effects that account for less than 1% of the variance in outcome (a moderately sized effect, assuming that G × E interactions and genetic main effects typically account for similar portions of variance in a phenotype; Duncan & Keller, 2011). Although it is generally appreciated that low statistical power can lead to Type II error, it can also increase the proportion of Type I errors reported in the literature. The third criticism of G × E studies is that there is insufficient correction for multiple testing and, consequently, inflated Type I error rates (Aschard et al., 2012), although this issue is hardly specific to research on G × E interactions (Simmons, Nelson, & Simonsohn, 2011).

A fourth criticism of G × E studies is that disparate exposures sometimes get called the same thing (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Uher & McGuffin, 2010). For example, "stressful life events" comprise self- and parent reports of early family environments, substantiated reports of maltreatment, composite measures of poverty, residential conditions, family structure, parental psychopathology, and physical illness. As a result, it is unclear whether failures to replicate G × E interactions should be attributed to measurement variance or to Type I error.

Although the G × E literature is characterized by a number of methodological shortcomings, it is not necessarily true that the identification and replication of statistical interactions between genotypes and environments should be the gold standard for determining whether or not a given G × E interaction is "real." Statistical interactions matter only insofar as they plausibly reflect some biological process. Convincing evidence for the biological plausibility of G × E interactions comes from research that uses a range of methods and models not only to document the presence of G × E (i.e., whether the statistical interaction replicates in independent samples and across model organisms) but also to probe potential neural substrates of the interaction (Caspi et al., 2010). For example, although there has only been mixed success in replicating the *MAOA* × Maltreatment interaction (Jaffee, 2012; Kim-Cohen et al., 2006), there is growing evidence that (a) *MAOA* genotype moderates the effect of early rearing experiences on aggressive behavior in experimental primate studies (Newman et al., 2005), (b) methylation of the *MAOA* promoter is associated with low levels of the MAOA enzyme (Shumay, Logan, Volkow, & Fowler, 2012) and low MAOA enzyme activity is associated with self-reported trait aggression (Alia-Klein et al., 2008), and (c) the *MAOA* variant is associated with the activation and connectivity of cortical and subcortical regions in response to negatively valenced stimuli and response inhibition tasks (Buckholtz et al., 2008; Meyer-Lindenberg et al., 2006; Passamonti et al., 2006). These findings make a case for the biological plausibility of G × E interactions involving *MAOA* and early rearing environments. Repeated exposure to negative experiences may potentiate a genetically based predisposition to aggressive behavior via corticolimbic circuits involved in emotion regulation, memory for affectively salient events, and impulsivity.

Findings from molecular genetic studies have limited clinical value thus far

One of the goals of basic research in developmental psychopathology is to translate findings on the etiology and course of psychopathology into policy and clinical practice. Behavioral geneticists share this goal. Many scientists hoped that the sequencing of the human genome in 2003 and subsequent discoveries of genes for disorders would inform genetic screening, drug discovery, and personalized medicine. These hopes have remained largely unrealized. The small size of most genetic risk factors has hampered efforts to identify an individual's risk for disease (Goddard & Lewis, 2010) and simulation studies have shown that case-control studies on the order of approximately 10,000 individuals would be required to identify a set of variants that would account for more than 50% of the genetic variance (Wray et al., 2007). Although it is accepted that there can be clinical utility in using genotype to predict disease risk, this is only the case for highly penetrant variants, such as the breast cancer Type 1/2 gene (*BRCA1/2*) loci that predispose to breast and ovarian cancer. For most multifactorial diseases, like Type II diabetes, nongenetic risk factors for complex diseases remain better predictors of disease status than genetic risk factors identified via GWA studies (Talmud et al., 2010) and genetic risk prediction for psychiatric disorder remains poor.

In the domain of personalized medicine, there has been little evidence, despite great initial excitement (Meyer et al., 2000), that either candidate gene variants or significant hits from GWAS modify patients' responses to antidepressant (Keers & Aitchison, 2011; Taylor, Sen, & Bhagwagar, 2010; Uher et al., 2010) or antipsychotic treatments (Malhotra, Zhang, & Lencz, 2012). The small effects of gene variants identified in GWAS and the observation that hundreds of variants of small effects may contribute to risk for disorder means that most GWA studies have been largely uninformative for drug discovery efforts (Cirulli & Goldstein, 2010).

Summary of molecular genetics research

In summary, there is an ongoing debate about the relative importance of common versus rare variants in predicting risk for disorder. Although GWAS have had some success at identifying genomewide hits, these variants typically account for a very small proportion of the variation in psychiatric disorders. There has also been success at identifying rare variants associated with highly heritable disorders like autism, schizophrenia, and bipolar disorder. These successes must be followed up by efforts to determine the function of likely causal variants. Although there is substantial interest in G × E interactions, there are ongoing challenges in this research area, including insufficient power to identify G × E effects, a poten-

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tially high false discovery rate, and a lively debate about what constitutes evidence of replication. Pharmacogenetic and genetic screening approaches must establish both clinical validity and utility in order to inform intervention. Doing so will involve translational efforts at different levels, of which the identification of risk variants, even in the most promising cases, is only the first step of many (McMahon & Insel, 2012).

Social Regulation of Epigenetics and Gene Expression

Although "gene–environment interplay" has typically referred to gene–environment correlations and interactions, it can also refer to social regulation of epigenetic and gene expression profiles. The DNA sequence is stable across cells and over time (but see Charney, 2012 for a critique of this conventional understanding), but gene expression (i.e., messenger RNA abundance) and the chemical modifications to DNA that promote and constrain gene expression (i.e., the epigenome) are highly dynamic across tissues, over time and through varying environments. Moreover, epigenetic and gene expression changes can be induced by the intracellular environment as well as the extracellular environment, including toxins, nutrition, maternal nurturing behavior, intrauterine factors, and stress (Cole, 2012; Jirtle & Skinner, 2007; Zhang & Meaney, 2010). The possibility that the environment "gets under the skin" to influence gene expression via epigenetic regulation with downstream effects on behavior challenges the conventional formulation of the skin as a barrier between the individual and the environment (Cole, 2012; Kendler, 2012).

The epigenome is highly dynamic and responsive to extracellular stimuli, which suggests that this area of research has the potential to be highly informative about the mechanisms underlying the development of normal and abnormal behavior, a key goal of research in developmental psychopathology. In the field of health psychology, researchers have already proposed a framework for understanding how adverse social experiences increase risk for chronic diseases of aging via epigenetic and posttranslational effects on immune function (Miller, Chen, & Parker, 2011). In psychiatry and behavioral pediatrics, researchers have also hypothesized that early experiences become "biologically embedded," with long-term implications for children's psychological well-being and psychopathology (Shonkoff et al., 2012).

At its most simplistic, gene expression refers to the process by which transcription factors inside the nucleus bind to regulatory elements in the gene to initiate RNA transcription, which may result in the translation of protein (Fu et al., 2007). The degree to which transcription factors and other regulatory proteins have direct access to DNA depends on chromatin structure, which is strongly influenced by epigenetic modifications, such as DNA methylation and histone modifications (methylation, acetylation, etc.; Mill, 2012). Epigenetic modifications explain how the DNA sequence, which is identical from cell to cell, can give rise to patterns of gene expression that vary dramatically across cells and how that variability can be stably maintained throughout development and cell proliferation (Jaenisch & Bird, 2003). We describe epigenetic and gene expression studies in turn.

Social regulation of epigenetic processes

Epigenetic processes that influence gene transcription include histone modifications and DNA methylation, the latter of which has been the focus of much of the recent work in epigenetics. Methylation refers to the addition of a methyl group to CG (CpG) dinucleotides that are sites in the genome where the nucleotide cytosine is followed by the nucleotide guanine and separated by only one phosphate. In general, DNA methylation can disrupt the binding of transcription factors (which stimulate gene expression) and attract methyl-binding proteins that are associated with gene silencing and chromatin compaction (Jaenisch & Bird, 2003).

Research on the epigenetic underpinnings of behavioral regulation was catalyzed by a series of animal studies conducted by Meaney, Szyf, and colleagues who were interested in maternal nurturing behaviors and their effects on offspring biobehavioral outcomes. Using a rat model of maternal behavior, they found that the offspring of mothers who engaged in high levels of licking, grooming, and arched-back nursing behavior were less fearful as adults and produced relatively lower levels of stress hormones (i.e., glucocorticoids and adrencorticotropic hormone) in response to being physically restrained (Liu et al., 1997). These effects of maternal behavior on offspring stress response were caused by reversible epigenetic changes to the glucocorticoid receptor (GR) gene that increased GR gene expression (Weaver et al., 2004, 2005) and by epigenetic changes to numerous other genes (Weaver, Meaney, & Szyf, 2006).

The publication of these papers and others generated enormous interest in how early adversity may increase risk for later psychopathology via epigenetic processes. Researchers have relied heavily on animal models (e.g., Mueller & Bale, 2008; Murgatroyd et al., 2009; Roth & Sweatt, 2011), but a growing number of studies use human tissue. For example, it has been shown that suicide completers with a history of childhood abuse have different profiles of hippocampal GR methylation (Labonte et al., 2012b; McGowan et al., 2009) as well as different methylation profiles across the genome (Labonte et al., 2012a) compared with suicide completers without a history of abuse. In a sample of newborns who provided cord blood, higher levels of methylation at a specific CpG site in exon 1F of the GR gene were observed among those whose mothers had higher levels of depressed and anxious mood in the third trimester (Oberlander et al., 2008). These methylation changes were also associated with increased cortisol in response to a visual information processing task at 3 months of age (Oberlander et al., 2008). Genome-wide methylation scans have identified higher methylation levels across a range of genes among adults who experienced high versus low levels of childhood socioeconomic disadvantage (Borghol et al., 2012), among adolescents who did or did not experience foster care (Bick et al., 2012), and among ado-

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lescents who experienced high versus low levels of family adversity in infancy and early childhood (Essex et al., 2013).

Social regulation of gene expression

Like epigenetic profiles, gene expression profiles are also socially regulated, providing a possible biological pathway by which the environment could increase risk for disease (Cole, 2012; Miller et al., 2011). For example, elderly adults who report feeling socially isolated are characterized by upregulation of genes involved in the inflammation response and downregulation of genes involved in responses to viral infections and in the production of antibodies (Cole et al., 2007). Thus, changes in gene expression induced by a perception of social isolation could increase an individual's risk for inflammation-related diseases such as cardiovascular disease. Other studies have shown that growing up in conditions of social disadvantage (Miller et al., 2009) and, particularly, perceiving one's social environment to be threatening (Chen et al., 2009) is associated with upregulation of inflammation-related genes, although a warm relationship with a parent can break this link (Chen, Miller, Kobor, & Cole, 2011). Primate studies in which social status (i.e., dominance rank) is experimentally controlled confirm and extend results from human studies, showing that genes involved in immune function were upregulated in primates of lower dominance rank and that changes in social rank were associated with corresponding changes in gene expression (Tung et al., 2012). Highlighting the interdependence of endocrine and immune systems, variation in gene expression in the majority of the rank-related genes was partly mediated by variation in tissue composition and glucocorticoid regulation (Tung et al., 2012).

Although this literature on the social regulation of gene expression has primarily dealt with inflammation-related physical health disorders (for which it is particularly valid to interrogate peripheral blood cells versus other tissues), dysregulation of the immune response is potentially involved in some psychiatric disorders (e.g., major depressive disorder; Raison, Lowry, & Rook, 2010) and in response to social stressors like maltreatment (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). The general mechanism is likely to apply to other psychiatric disorders. Interestingly, gene expression and epigenetic profiles show allele-specific patterns (Cheung & Spielman, 2009; Lee, 2012; Meaburn, Schalkwyk, & Mill, 2010). If some gene variants are more susceptible to social regulation than others, then corresponding alterations in gene expression or epigenetic modifications could provide a potential mechanism by which genes and environments interact to influence health and disease (e.g., Tung et al., 2011).

Challenges to research on epigenetics and gene expression

Despite the excitement generated by the linking of early (and ongoing) life experience with epigenetic and gene expression profiles, this research faces numerous challenges (Heijmans & Mill, 2012). The primary challenge concerns the human tissues available for research in psychiatry. Psychiatric disorders are typically disorders of the brain, but brain tissue is obviously not readily available from live human subjects. Therefore, researchers either obtain archived brain tissue from deceased subjects or peripheral tissues (usually whole blood cells) from live human subjects. Both approaches are problematic. Information about brain donors is usually limited to what is known from medical and coroner records or from individuals who were related to the deceased and who may be unreliable informants. Thus, information about an individual's early experiences may be limited. Moreover, interpretation of gene expression or epigenetic profiles in postmortem brain tissue is complicated by clinical, gender, aging, tissue, and other factors (Atz et al., 2007). Conversely, although obtaining peripheral tissues from live human subjects is a relatively noninvasive process, it is uncertain that the gene expression or epigenetic profile of those tissues is similar to that of brain or other tissues (Heijmans & Mill, 2012; Rollins, Martin, Morgan, & Vawter, 2010). For example, depending on where in the genome methylation levels are being interrogated, correlations across tissue types (including brain and blood tissue) vary substantially (Davies et al., 2012). Further, certain genes whose expression is restricted to only neurons or glia will necessarily be inaccessible from the periphery.

Apart from the challenge of identifying relevant human tissues, additional work is needed to determine whether within-individual and between-group differences in epigenetic profiles are associated with corresponding changes in gene expression and, similarly, whether changes in gene expression correspond to altered protein products. Finally, epigenetic and gene expression effects are typically small in magnitude, and it is unclear what the biological significance of such small alterations is (Heijmans & Mill, 2012).

Despite these challenges, there is scope for studying the social regulation of epigenetic and gene expression profiles in humans, with one goal being to identify clinically relevant biomarkers of early and/or ongoing adversity. Although acquisition of blood samples from children is not trivial, blood may represent the tissue source with the most potential to contain a predictive biomarker. An evaluation of gene expression profiles comparing patterns in blood and brain identified over 4,100 transcripts that were expressed in both compartments (Rollins et al., 2010). Further, it has been shown that plasma levels of brain-derived neurotrophic factor (BDNF) are highly correlated with brain levels of BDNF (Klein et al., 2011), supporting the potential utility of this approach. Importantly, some progress has been made toward the identification of acute biomarkers for mood disorders (Le-Niculescu et al., 2009) and schizophrenia (dopamine and cyclic AMP regulated phosphoprotein-32; Torres et al., 2009). Therefore, analysis of DNA methylation profiles and/or gene expression in blood has the potential to identify a predictive risk biomarker, and discovery efforts in this domain should be pursued.

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Summary

In summary, research on social regulation of epigenetic and gene expression profiles offers exciting possibilities for developmental psychopathology researchers who are interested in both the timing and episodic course of psychopathology. Because epigenetic and gene expression profiles are highly dynamic (unlike the genome itself), they offer a plausible biological mechanism by which changing exposures over time could affect the course of disorder. Repeated measurement of DNA (preferably from whole blood), exposures, and outcomes could be used to show how epigenetic or gene expression profiles vary over time in response to changes in exposures and whether these track the course of disorder. This work would require careful consideration of the density and timing of measurement to optimize chances of observing hypothesized associations.

What the Role of Behavioral Genetics in Developmental Psychopathology Is Going Forward

Using behavioral genetics to hone our understanding of causal exposures

Developmental psychopathology is concerned with understanding the etiology and course of normal and abnormal development (Sroufe & Rutter, 1984), and this goal is undercut in the absence of information about whether identified risk and protective factors are actually causal. Twin and adoption studies remain relevant because they can serve as natural experiments that provide important information about the causal status of environmental exposures as well as the biological substrates of disorder. The discordant MZ twins design is a particularly powerful tool for identifying risk factors for disease because MZ twins are matched for age, sex, genetic background, and shared family experiences (van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012; Vitaro, Brendgen, & Arsenault, 2009). For example, MZ twins who are discordant for the experience of having been bullied show different profiles of cortisol reactivity to a psychosocial stressor, with the bullied twin in a pair showing a blunted cortisol response in comparison to his or her nonbullied co-twin (Ouellet-Morin et al., 2011). Discordant MZ pairs also provide information about whether changes in gene expression or epigenetic profiles are associated with disease phenotypes (Kuratomi et al., 2008; Rosa et al., 2008). Although exposure–outcome associations detected in the discordant MZ twins design do not necessarily imply a causal association, the combination of the discordant pairs approach with other quasiexperimental and statistical matching methods does allow for stronger causal inference (Kendler & Gardner, 2010).

Like the discordant MZ pairs approach, the children of twins design provides information about the extent to which familial confounding accounts for observed associations between risk factors and outcomes (e.g., D'Onofrio et al., 2007; Knopik et al., 2006). Adoption studies not only shed light on the degree to which experiences in the family have genetically versus environmentally mediated effects on children's behavior and abilities, but they can also be informative about the unique effects of the prenatal environment on children's outcomes if the child's biological mother reports on her behavior during pregnancy (Neiderhiser et al., 2007).

Using behavioral genetics to understand the dynamic nature of risk factors for the development of psychopathology

The discipline of developmental psychopathology is intrinsically concerned with transitions between normal and abnormal functioning over time and with identifying factors that either minimize or enhance the likelihood of such transitions occurring. This research effort requires that researchers study individuals and their environments longitudinally in order to link changes in risk or protective factors with changes in functioning. For example, Gerald Patterson's work with the Oregon Social Learning Center showed how escalations in harsh and coercive interactions between parents and children amplified difficult or hard to manage child behaviors into clinically significant conduct problems (Patterson, DeBaryshe, & Ramsey, 1989).

Behavioral geneticists can contribute to this research effort by delineating change over time in gene expression and epigenetic profiles. For example, blood samples taken repeatedly over key developmental transitions (e.g., the transition to puberty) and assayed for gene expression or methylation profiles could be informative about the biological correlates of normal or abnormal behaviors that typically emerge during that period (e.g., the emergence of depressive disorder among adolescent girls). Such an approach would be particularly informative in conjunction with efforts to trace changes over the same period in risk and protective factors in the environment that might be regulating the genome or the epigenome (e.g., the presence or absence of socially supportive relationships). Observed associations could be followed up with experimental work to determine whether risk and protective factors were causally related to biological changes. For example, gene expression profiles could be measured before and after randomized controlled cognitive behavioral interventions designed to prevent depression. Such research would be characterized by the limitations outlined earlier, but it could provide a starting point for thinking about how developmental changes at all levels of the individual and his or her environment result in transitions into and out of psychopathology.

Bridging from behavioral genetics to neuroscience and psychology

Understanding the development of normal and abnormal behavior ultimately involves tracing paths from genes to brain to behavior and understanding where and how social experiences intersect these pathways. Behavioral genetic studies that identify associations between genes and behavior provide

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a starting point in this endeavor. Ultimately, however, delineating the causal mechanisms that underlie the etiology and course of normal and abnormal phenotypes will require both top-down and bottom-up approaches that span a variety of disciplines.

Imaging techniques. Neuroimaging genetics is one promising approach to identifying connections between genes, brain function, and cognitive phenotypes that underlie disorder (Bigos & Weinberger, 2010; Hariri et al., 2002; Meyer-Lindenberg, 2012). The goal of imaging genetic studies is to determine whether candidate gene variants (involved in neurotransmitter systems that are associated with clinically relevant cognitive phenotypes) are associated with individual differences in brain activity. For example, a meta-analysis of genetic imaging studies identified an association between genotypic variation in the serotonin transporter linked polymorphic region and amygdala activation to negatively valenced stimuli, such that carriers of the short allele were more reactive to negative versus neutral stimuli than were carriers of the long allele (Munafo, Brown, & Hariri, 2008).

Imaging genetic studies have several advantages. First, functional MRI (fMRI) studies are relatively noninvasive. Second, the penetrance of common SNPs for neuroimaging phenotypes is greater than for other neuropsychological phenotypes (Flint & Munafo, 2007), meaning that sample sizes do not need to meet the requirements of GWAS in order to identify hypothesized effects. However, imaging genetic studies also face a number of methodological and conceptual challenges. Currently, the bioinformatics tools are not in place to model the influence of multiple genes or Gene × Gene interactions (i.e., epistasis) on imaging phenotypes (Meyer-Lindenberg, 2012). Like GWAS, fMRI studies are correlational. Moreover, they identify associations between gene variants and individual differences in regional brain activation but not in specific neurotransmitter systems that would potentially be more informative about the mechanisms by which gene variants were associated with brain function. Third, relatively few imaging genetic studies have involved pediatric samples (Pine, Ernst, & Leibenluft, 2010). Given that many disorders studied in adulthood have their origins in childhood, imaging genetic studies of both healthy children and diagnosed children would be informative about whether associations between genotype and brain activation change over time and whether these predate the onset of disorder.

In contrast to fMRI studies, positron emission tomography offers the opportunity to study specific neurotransmitter systems by imaging the binding density of specific neurotransmitter receptors as well as neurotransmitter concentrations, which can be informative about the pathophysiology of disorder as it relates to specific gene variants (Willeit & Praschak-Rieder, 2010). In this case, radioligands (i.e., compounds that bind selectively to receptors of interest) are administered intravenously to determine whether receptor binding site densities or enzymatic activity vary across groups (e.g., cases versus controls or genotype groups). For example, being homozygous for the methionine allele of the catechol-*O*-methyltransferase Val^{158}Met gene is associated with cognitive decline in Parkinson disease patients and with activation in cortical regions that are hypothesized to subserve executive function via the regulation of synaptic dopamine levels by catechol-*O*-methyltransferase (Williams-Gray, Hampshire, Barker, & Owen, 2008). Subsequent neuroimaging work using fluorodopa positron emission tomography showed that methionine homozygotes had significantly higher levels of presynaptic dopamine in frontal regions (Wu et al., 2012), thus providing a potential mechanism by which genotype could give rise to observed cognitive deficits.

What Will Facilitate Advances in Behavioral Genetic Research?

Bridging animal and human models in behavioral genetics research

Although there is a long history of using animal models in behavioral genetics research, this line of work has proceeded largely in parallel with human studies. The field would benefit enormously from a more integrative approach in which teams of researchers could move flexibly between human and animal models.

First, animal studies allow for a level of experimental manipulation that is not possible in human research. For example, consider the epidemiological finding that poor nutrition in pregnancy is associated with a range of psychiatric phenotypes. In humans, this association has been detected in studies that correlate mothers' self-reports of her nutrition and psychiatric symptomatology (controlling for any variables that might confound the association) and in rare circumstances when an entire population has experienced severe nutritional deprivation (e.g., the Dutch Hunger Winter; Susser & Lin, 1992). Animal models allow for greater leverage in identifying causal effects of maternal diet on offspring outcomes because the timing and the quality of prenatal nutrition variables can be manipulated experimentally. For example, the offspring of animals fed a high-fat diet during pregnancy and lactation not only are heavier at birth than the offspring of animals fed a control diet, but they also show differential methylation of opioid and dopaminergic genes in the mesocorticolimbic reward circuitry, which is implicated in the consumption of palatable foods (Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010). Another study showed that the offspring of Japanese macaques who were fed a high-fat diet during pregnancy showed differential expression of serotonergic genes in the rostral and caudal dorsal raphe nucleus and elevated rates of anxious behaviors compared with the offspring of mothers fed a control diet (Sullivan et al., 2010). Thus, the experimental study of animals affords opportunities to manipulate the timing, duration, and severity of exposures and to identify biological mechanisms that mediate effects of exposures on behavior. Moreover, given

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shorter gestations and accelerated development in many animal species compared to humans, it is relatively easy to follow animals longitudinally or to do cross-sectional studies of cohorts at different stages of development in order to probe the effects of risk exposures over time and across multiple levels, from the biological to the behavioral.

Second, human and animal studies can be mutually informative. For example, there is a robust association in human epidemiological studies between prenatal exposure to alcohol and adverse motor, perceptual, cognitive, and behavioral outcomes in offspring, most notably fetal alcohol syndrome (Clarren & Smith, 1978; Huizink & Mulder, 2006). These epidemiological findings are bolstered by experimental data from multiple animal models, including mouse, rat, and primate, that identify causal effects of high doses of alcohol in utero (Schneider, Moore, & Adkins, 2011). Moreover, experimental animal studies have extended findings to show effects of prenatal exposure to alcohol on neural development, including dopamine receptor density in primate striatum (Roberts et al., 2004) and multiple effects on the dopamine system as identified in rodent studies (for a review, see Schneider et al., 2011). Follow-up work in humans could test whether the association between alcohol exposure and dopamine receptor density replicates and whether it potentially mediates effects of in utero alcohol exposure on hyperactivity.

The success of efforts to move between animal and human models hinges on identifying outcomes that are translatable across species (e.g., hyperactivity) and on tissues that can be readily interrogated across species; placenta, amniotic fluid, and cord blood exist that may eventually prove to contain informative biomarkers of adverse clinical outcomes in children. These tissues are readily available, and therefore worthy of investigation. The placenta represents a critical interface between the mother and developing fetus, providing nutrients as well as participating in the removal of toxins or waste. Messenger RNA profiling has successfully been used to identify altered gene expression in placentas from babies with altered birth weights (Mannik et al., 2010; Mericq et al., 2009). Amniotic fluid contains cell-free fetal nucleotides (DNA and RNA), which derive from the fetus and which represent a potentially rich source of information on the state of fetal gene expression. Therefore, specific gene expression changes within these tissues may be associated with in utero exposure to alcohol and may also be predictive of adverse neurobehavioral outcomes in the offspring.

Despite promising avenues for research, there are substantial challenges in translating findings across species. Many of the risk factors that are most robustly associated with human psychopathology are multifactorial, such as social disadvantage or stressful life events. In these cases, human researchers working together with animal researchers will need to generate specific hypotheses about the "active ingredients" of these exposures that can be replicated in animal models (e.g., uncontrollable exposure to aversive stimuli, stable and unstable dominance hierarchies).

Interdisciplinary training

Although there are many developmental psychopathology researchers who embrace a biopsychosocial model of development and who are interested in integrating genetics with social and clinical science, it has, historically, been difficult to get interdisciplinary training and to do interdisciplinary research. This issue is increasingly relevant as more and more epidemiological cohort studies with strong social science orientations have collected and banked biological samples from their participants (Relton & Smith, 2012). On many college and university campuses, collaboration between geneticists and developmental psychopathologists is hindered by several factors. Most geneticists do not study psychiatric disorders nor are they epidemiologists. They study the mechanisms of genes that underlie physical health problems, such as cancer or diabetes or cardiovascular disease. Many of them study the genetics of zebra fish, fruit flies, or even yeast and think about the environment as nothing more than a source of error variation. Under these circumstances, developmental psychopathologists and geneticists not only lack common methods, but they also lack a common phenotype, a common understanding of (or interest in) the course of disorder, and, in some cases, a common appreciation for how distal environments like social status or proximal environments like parental care interact with genetic influences on development.

The good news is that interdisciplinary training is increasingly available. Several research centers, such as the Social, Genetic, and Developmental Psychiatry Centre at King's College London, the Institute for Behavioral Genetics at the University of Colorado, Boulder, and the Virginia Institute for Psychiatric and Behavioral Genetics, offer graduate training in quantitative and molecular genetics and include developmental psychopathology researchers among their faculty. There are numerous summer school and training courses for researchers interested in learning more about quantitative behavioral and molecular genetic techniques. Interdisciplinary training, particularly for research that crosses human and animal models of disorder, could be enhanced through the development of NIH pre- and postdoctoral training programs wherein students would have the opportunity to forge links between researchers addressing similar questions from different levels of analysis.

Consortia

A notable feature of genetic epidemiology is the degree to which it is a collaborative enterprise. For meta-analytic studies of GWAS, it is not unusual for a dozen or more research groups to pool their data. This has happened for two reasons. First, researchers themselves have recognized that the sample sizes required for well-powered genetic studies exceed the resources of any one team. Second, academic journals have set increasingly stringent standards for genetic evidence that researchers can meet more successfully by pooling resources. Funding agencies recognize the need to make datasets available in pub-

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lic repositories so that they can be exploited as fully as possible. Meanwhile the industrialization of genetic technologies has given rise to economies of scale, concentrating data collection and analytic expertise in specialist centers whose scientists are well placed to conduct and coordinate consortia.

Conclusions

As a discipline, developmental psychopathology is concerned with the study of normal and abnormal behavior, with identifying factors that explain the etiology and course of psychopathology, with the study of risk mechanisms at multiple levels of analysis, and with susceptibility to and escape from risk. These concerns fall squarely in the domain of behavioral genetics as well. Behavioral genetic approaches facilitate causal inference in nonexperimental studies because they can rule in or out alternative explanations for observed associations between exposures and outcomes, namely, that these are genetically mediated. Determining the causal status of risk factors is a crucial step in the road to uncovering the mechanisms by which they increase susceptibility to disorder. Moreover, findings from quantitative and molecular genetic studies have laid the groundwork for research that aims to identify gene function and to trace pathways across multiple levels from genes through the brain to behavior. These efforts will be facilitated by increased interdisciplinary training and collaboration among epidemiologists, neuroscientists, and cellular and molecular biologists working across human and animal models of disorder. Although the clinical implications of genetics research have not been fully realized, there is hope that the identification of rare variants and the potential for sequencing studies to identify functional mutations will prove informative about the biological substrates of disorder and will suggest drug targets.

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