

Chapter 2

Genetics, Behavioral Intervention, and Human Development

David Reiss

This book explores the role of new findings in genetics to more fully understand development across the life span. It gives equal attention to the role of genetic studies in identifying new targets for interventions and the sources of individual differences among individuals in their response to interventions. In the last decade, there have been a number of publications that have reawakened interest in this interplay between genetics and behaviorally relevant interventions but this interplay began almost as soon as there were tools to study genetic influences on behavior.

The ancients had already mastered practical genetics through their artful use of selective breeding. They learned that complex patterns of behavior were highly heritable. For example, corgis were bred as cattle herders and could be relied on to circle their herd and barking to keep them together; indeed, this trait readily generalizes to herding humans who are also herded when hiking, walking, or even swimming. Selective breeding is central to Darwin's *Variations in Plants and animals under domestication* (Darwin, 1920 (1868)) who notes the accomplishments of Plato, Alexander the Great, and Virgil.

Scientific genetics began with Mendel's famous pea experiments. Though the main results were published in a well-known journal in 1866 (Mendel, 1948 (1866)), they were little noticed until highlighted by the German botanist, Correns (1950), in 1900. Mendelian patterns of inheritance became widely explored and understood in many areas of science.

Among its most notable applications to human development was the discovery of phenylketonuria by Asbjorn Folling in 1932 in two siblings afflicted with severe developmental delays and mental retardation (Centerwall & Centerwall, 2000).

D. Reiss (✉)

Yale School of Medicine, Child Study Center,
P.O. Box 207900, New Haven, CT 06520, USA
e-mail: david.reiss@yale.edu

Folling was born and raised in rural Norway but unusual among his rural peers in those days, achieved entry into a technical college where he studied chemistry and then completed medical training at the University of Oslo. Folling was the last station in an agonizing search by the children's parents, Borgny and Harry Egeland, for the causes of their children's severe behavioral problems. Folling has described how he added ferric chloride to these children's urine—as a test for ketones ordinarily found in diabetes—and watching it turn green, a reaction he had never seen. Folling used his background in chemistry to identify the abnormal urinary substance as phenyl pyruvic acid. When he found eight additional cases after a survey of 400 institutionalized children, he published his results in 1935. Folling understood Mendelian genetics well enough to deduce that the parents must be heterozygote carriers and indeed published the first report on how to detect their status with a phenylalanine challenge test (Sydnes & Følling, 1962).

The most pivotal work, relevant to this chapter, subsequent to Folling's original discovery, was the testing of a low phenylalanine diet by Horst Bickel a German trained physician who was training as pediatrician in Birmingham University (UK) Children's hospital. In a single 2-year-old girl, he reduced and then augmented phenylalanine in her diet and demonstrated the partial reversibility of the somnolent retardation that was well established in this toddler (Bickel, 1953). The experiment can be witnessed on You Tube (<https://www.youtube.com/watch?v=-rs0iZW0Lb0>). Folling's ferric chloride test was used for some time and could reveal the disease if applied to a baby's diaper; however, it was often not positive until well after the typical newborn left the hospital and might be lost to screening. Therefore, the final step in this story—for our purposes—is the perfection of a blood test for PKU that would reveal the disease in newborns while they were still in the hospital for screening. Robert Guthrie a physician and microbiologist, working at Buffalo Children's Hospital, took advantage of the singular ability of phenyl pyruvic acid to foster the growth of *Bacillus subtilis* in a restricted culture medium (Guthrie & Susi, 1963). The availability of highly specific and sensitive test as well as an effective dietary treatment, if started very early, led to legislation in all 50 states and the District of Columbia requiring all hospital-born infants to be screened.

Both Gregor Mendel and Asbjorn Folling were, in some sense, fortunate. Their agricultural and clinical experiments focused on a highly heritable phenotype where one gene determined one distinctive phenotype. In Folling's case, the gene was not expressed in the exceptionally complex organ of the brain but chiefly in the liver. Moreover, a straightforward environmental treatment, diet, could fully compensate—or nearly so—for the disease's prime deficiency.

Implicitly, the PKU success story has set high hopes that the genetic etiology of a range of disorders is that are more complex than PKU will yield a set of biological targets that could be discovered in practical programs of screening and that either pharmacologic or behavioral interventions might either correct or compensate for the basic deficiencies of the disorder. The *genetic delineation of targets for intervention* will be one of the two themes of this chapter and we will return to it to survey accomplishments thus far and anticipate the future.

The one-gene, one disorder paradigm has successfully uncovered other screenable and treatable inborn errors of metabolism but, in its simple form, is not applicable to the complex syndrome of behavioral disorders or of behavioral health that have been delineated over the decades (for the phenomenology and genetics of positive syndromes of well-being, see National Research Council, 2013; Rietveld et al., 2013). However, another line of genetic research contributes to our understanding of behavioral interventions. Ten years before Folling's first Norwegian publication, a graduate student of Lewis Terman—Curtis Merriam—was the first to utilize the twin method for estimating more global effects of genetic influence on human behavior; his interest was in the full range of mental abilities rather than severe retardation. However, Merriam lacked a secure method for distinguishing monozygotic from dizygotic twins, a strategy that was developed by a German dermatologist Herman Siemens (Rende, Plomin, & Vandenberg, 1990) who developed criteria for their distinction that presages those still used today (Siemens, 1927). Siemens was passionate believer in heredity long before he first used twins to more precisely calibrate its effects on both skin disease and behavior. In the deep dismay that swept post-World War I Germany he inadvertently helped fan a growing enthusiasm for eugenics that fueled a hope for the restoration of German racial superiority (Proctor, 1988). The worldwide revulsion at this mixture of racism and genetics suppressed research on the genetics of human behavior for a generation following World War II.¹

The post-World War II revulsion against eugenics rendered all genetic research on human intelligence and behavior suspect and added implicit weight to objections to the twin method. Critics wedded with equal fervor to a fully environmentalist position underscored the many ways in which MZ twins were treated more similarly than DZ twins, hence upending the basic assumption of the method that the environments of MZ and DZ twins were equally correlated (the equal environments assumption). However, a series of studies using twins reared apart served as a rigorous test of this assumption and clarified the strengths of the twin method.²

Long before the controversy surrounding the twin method was resolved investigators recognized that this method could help them learn more about behavioral intervention. The first of these was Arnold Gesell who trained first as a psychologist and then, while completing his medical degree at Yale, founded its Child Study Center. Gesell recognized that he could use monozygotic twins to control the effects of genetic influences not just on naturally occurring behavior as a phenotype but on *response to treatment* as a distinctive phenotype. Thus, Gesell trained one member of a toddler MZ pair to climb stairs and used the other as a control. Thus, he held constant the effect of genetic influence on the children's *response to treatment*. He also held constant the effects of their correlated environments (e.g., their mother's personality). In Gesell's summary of this co-twin control method (Gesell, 1942), he

¹ Siemens was appointed chair of dermatology at Leiden before the outbreak of World War II and, objecting to Nazi occupation procedures, was jailed by the movement he inadvertently helped to foster (Burgdorf, Bickers, & Hoenig, 2014).

² For a full review of this controversy and its resolution, see Reiss (2016).

clarified that his method could also be used to clarify the points in development in which intervention might be most effective.

In sum, Folling used genetic inquiry to delineate a biochemically identified target for intervention. His specific discovery was to identify the urinary abnormalities of his child subjects through chemistry alone. But his presumption that a single gene caused the disorder and his knowledge that Mendelian genetics were crucial to his identifying parents who were carriers. Gesell first formulated the idea that genetic analysis could account for *variations in response to treatment*. Gesell chose to control these influences but later investigators chose to estimate more directly the effects of genotypic variation on response to behavioral intervention.

The first study in this genre, following Gesell, was by Paul Fox and his colleagues using the widely publicized sample of twins reared apart that were recruited worldwide to the University of Minnesota (see Bouchard, Lykken, McGue, Segal, & Tellegen, 1990 for a summary of this study). As part of a lengthy assessment period Fox observed his subjects learning to improve their performance on a pursuit rotor task and correlated separately the performance of 64 MZ twins and 32 DZ twins all reared apart (Fox, Hershberger, & Bouchard, 1996). The most critical comparisons were for slopes of performance across days; the slope reflects rate of change in response to practice. For example, MZ twins had an intraclass correlation of .56 for the magnitude of this slope and DZ twins a correlation of .24 suggesting that heritability and sibling-specific environments accounted equally for difference in *rate of learning*. What might have been the results had the twins been reared together? Would there have been any evidence of a shared or between family effect on rates of learning intervention and practice of the rearing environment the twins had shared together? Follow-up studies have been surprisingly rare but two suggest there would have been little difference between twins reared together and apart (Missitzi et al., 2011, 2013). Experiments with children might show a more notable effect of the shared rearing environment.

It is surprising how infrequently the twin design has been used to explore the balance between environmental and genetic factors that contribute to success or failure of behavioral interventions. Indeed, the twin method can be used not only to clarify the balance between anonymous genetic and environmental influences but also to track down, quite specifically, what those factors might be. For example, the heritability of men's capacity to remain abstinent—once they commit to stopping tobacco—is highly heritable. Likewise, the intensity of nicotine withdrawal symptoms is also heritable though less so. Of special interest is that the genetic influences for withdrawal and for difficulty in maintaining abstinence overlap (Xian, 2003) providing not only an important clue for refining or improving cessation programs but for searching for specific genes involved (Uhl et al., 2008).

To summarize, not long after developmental science acquired the tools for exploring genetic influences, investigators explored two lines of inquiry exploiting those tools to improve intervention. The research on PKU became a paradigm for the use of genetics to *better define targets for both preventive and therapeutic intervention*. Heterozygote parents, according to this vision, might be identified and provided genetic counseling, and infants with both recessive genes could be economically identified shortly after birth and provided with a specific environmental treatment whose mechanism of action

was clear compensatory rather curative, a distinction that remains important in both pharmacological and behavioral therapeutics. The prescient work of Gesell and a generation later of Fox, Bouchard and their colleagues suggested a second line of work: *genetic analysis of variations in response to treatment*. This work did not solidify into a paradigm. The twin method—and its companion, the adoption method—are powerful and rarely used tools for understanding behavioral interventions. But, as we will see, in unrelated developments, a growing interest in how specific genes moderate the effects of environmental influences has reawakened an interest in genetic influences on response to behavioral treatments. Likewise, the twin and adoption method has made a steady, if unheralded, contribution to defining targets for behavioral intervention in ways Gesell, Fox, and Bouchard could not have imagined. Each of these lines of investigation inevitably led to an expanded knowledge of developmental processes. Horst Bickel's 2-year-old PKU patient brightened up in response to reduce phenylalanine in her diet: her face expressed interest in dangling keys that her eyes followed closely, she climbed a chair that had been insurmountable on a normal diet and anyone watching the film would feel her retreat into the doldrums of retardation once the phenylalanine was added again to her diet. But she remained severely retarded throughout these trials; indeed, these trials underscored a critical period, very early in development, for the establishment and restoration of basic functions of the brain. Critical periods were also of prime interest to Gesell and to those few investigators who followed his lead in using the co-twin control design. Gesell's lifelong scientific passion was mapping the developmental stages and landmarks of typical development. The MZ co-twin control design enabled him to hold constant individual differences among children occasioned by their genetic differences and differences in environmental factors common to siblings in the same family. It was a strategy that helped him identify the developmental stages that were common for all children he studied. It is a pity that investigators lost interest in the use of twins by the advent of World War II. As we sketch two uses of genetics in intervention research—identify targets and exploring individual differences in response—we will suggest ways in which newer research can unravel some seemingly intractable research problems in development.

Defining Targets for Behavioral Intervention

As noted, PKU research introduced a paradigm for the use of genetic information for therapeutic intervention, specifically for environmental alteration of genetic risk. However, PKU reflects the effects of a polymorphism of a single gene regulating the activity of a liver enzyme. Without major modification, this paradigm cannot be applied to disorders influenced by many genes each of which may have pleiotropic³ effects on brain mechanisms and each of which are densely interrelated with other mechanisms and are also influenced by social and other environmental influences as well. Nonetheless, this paradigm has potential and we review here directions for research within its frame.

³When allelic variation in a single gene affects two or more distinctly different phenotypes that are unrelated to each other, the variation is set to be pleiotropic.

Defining Groups of Individuals at Risk for Disease

The PKU paradigm suggests that if we can identify groups of individuals at risk for a disorder before the disorder occurs we may prevent it even if we do not fully understand its pathogenesis. For example, Uhl and his colleagues have extended his work on assessing genes that favor successful cessation of smoking following a planned intervention. These—combined in polygenic risk score—postdict which adolescents at age 14 will rapidly escalate drug use into adulthood and which adolescents will, by and large, resist the addictive substances (Uhl, 2014). Uhl did not test whether his polygenic risk score overlapped or exceeded in precision that of a simpler family history of smoking. However, Daniel Belsky and colleagues using a similar postdiction strategy with a somewhat different polygenic risk score found family history and genetic data independently contributed to the precision of postdiction (Belsky, 2013). That is, they used a polygenic risk score to distinguish which children became smokers and which did not across nearly 30 years of observation. However, great caution is necessary in identifying individuals at risk with polygenic risk scores. For example, Gartner and colleagues using a polygenic risk in a simulation model found no advantage over family history in screening for adolescent smokers (Gartner, Barendregt, & Hall, 2009). Further, broad experience with these genetic strategies in prediction obesity, cardiovascular disease, and diabetes has suggested they have little utility beyond a family history (Evaluation of Genomic Applications in & Prevention Working, 2010; InterAct Consortium et al., 2013; Veerman, 2011).

Belsky and Uhl used polygenic risk scores to postdict *patterns of behavior, poor self-regulation, and addiction*. However, this same strategy can be used to predict *sensitivity to environmental influences*. For example, gene variants regulating various CNS neurotransmitter systems postdict the responsiveness of adolescents to parenting style: favorable parenting in these adolescents was associated with enhanced self-regulation but those with unfavorable parenting developed serious problems in self-regulation; those without these so-called plasticity variants showed little effect of parenting either way (Belsky & Beaver, 2011). The role of these polygenic scores as practical screening is untested but promising.

Suppose a single gene or a set of genes reliably predicted a health outcome what is the prospect that a behavioral intervention might offset that risk analogous to the salutary effects of low phenylalanine diet in PKU? In two related proof-of-concept studies, Brody and his colleagues reported that a serotonin transporter gene polymorphism postdicted a higher risk in teens for a range of risk behavior (Brody, Beach, Philibert, Chen, & Murry, 2009) and a set of additional genes regulating gabaergic and dopaminergic brain function postdicted an increased risk for alcoholism (Brody, Chen, & Beach, 2013). In each case a brief, family-oriented prevention curriculum offsets these genetic risks. Additional information about these studies can be found elsewhere in this volume. While needing replication, these findings are important because they suggest that public health oriented interventions might, in some fashion, offset risk for serious disorders that are identified through genetic assays.

Quantitative genetics provides two useful tools for identifying groups of children at risk. The first is to identify the earliest appearing behavioral indicators of genetic

risk, in infants or toddlers. A powerful tool is the prospective adoption design where children are placed for care at birth, their development is followed across time, and detailed studies are made of both biological and rearing parents. Though prospective adoption studies are very rare, properly designed they can answer an important question: if one or both parents exhibit severe psychopathology what is the first manifestation of this risk in infants and toddlers? The Early Growth and Development Study is the only prospective adoption design to include birth parents, adopted parents, and children placed for adoption within a short time after birth (Leve, Neiderhiser, Scaramella, & Reiss, 2010) and to focus on social and emotional development in children. It has found three characteristics of toddlers that are very early manifestation of the genetic risk for externalizing disorders (as indexed by the psychopathology of their birth parents correcting for intrauterine factors): an inability to self sooth in frustrating situations, a need for structured parenting, and a capacity to evoke maternal negativity, especially in the context of marital difficulties (Fearon et al., 2014; Leve et al., 2009, 2010). The practical utility of these discoveries is untested but the findings suggest psychosocial interventions that may directly address these early psychological and interpersonal difficulties of children who are at risk for a broad variety of externalizing disorders including smoking and substance abuse.

A second contribution, drawn mainly from twin designs, is to identify natural environmental variation that has a major impact on behavioral development independent of a child genotype. These naturally occurring variations are good clues for innovative interventions. For example, little noted in the genetic literature is redundant evidence that sibling relationships differ in both warmth and conflict across families and these between-family differences regularly anticipate the development of both aggression and substance use in both siblings (Natsuaki, Ge, Reiss, & Neiderhiser, 2009; Neiderhiser, Marceau, & Reiss, 2013; Reiss, Neiderhiser, Hetherington, & Plomin, 2000a; Slomkowski, Rende, Novak, Lloyd-Richardson, & Niaura, 2005). The value of genetic information here is that it identifies these substantial influences as operating entirely by environmental mechanism and invites sibling-focused preventive interventions as part of an effective strategy for prevention.

Delineating Malleable Mechanisms of Gene Expression

The mechanisms by which genes are expressed in behavior are being defined on at least three levels.

The most familiar level is the molecular one where technical progress now allows a broad genome scans of patterns of methylation and expression of messenger RNA. Following the path breaking work of Meaney and Szyf in rats (see a review Meaney & Szyf, 2005 and material elsewhere in this volume), evidence is accumulating that adverse experience in both childhood and adulthood can alter patterns of gene expression as examined in postmortem brain samples (McGowan et al., 2009) and in peripheral blood (Cole et al., 2007). Although stressful circumstances can induce very distinct and contrasting gene expression profiles in circulating white cells and in brain

(Provencal et al., 2012), peripheral blood has yielded fairly consistent patterns of upregulated (genes regulating inflammatory responses) and downregulated (cortisol monitoring systems and antiviral mechanisms) expression systems, all of which heighten liability to a range of medical disorders (Cole, 2014; Miller et al., 2009). Preliminary, proof-of-concept trials suggest that cognitive behavior (Antoni et al., 2012) and mediation procedures (Bhasin, 2013; Creswell et al., 2012) can reverse some of these stress-induced profiles of gene expression. However, even in preliminary studies, it remains unclear how important these reversals are to patient recovery.

A second level of study is influence of genetic allelic variation on brain function. For example, two early publications in this field by Ahmad Hariri engendered considerable excitement: he and his colleagues reported that research subjects with one or two of the “short” versions of the serotonin transporter gene had stronger amygdala responses to emotional stimuli on fMRI (Hariri et al., 2002, 2005). This finding might explain why individuals with the short allele of this gene would be vulnerability to stress-induced depression as illustrated by the oft-cited paper by Caspi et al. (2003). However, many subsequent efforts to replicate this finding suggested that the effect of the single gene was, at best, very small (Murphy et al., 2013). The use of genetic variation to delineate the role of brain function in the pathogenesis of mental disorders will almost certainly have to examine the effects of many genes acting in concert and study variation in the function of neural networks and not single brain regions (Birnbaum & Weinberger, 2013).

Despite uncertainties in this field of study, the use of genetics to identify brain functions on the path to major disorders is an inviting target for behavioral therapeutic and preventive interventions. The most specific behavioral interventions are fMRI neurofeedback techniques where subjects learn to control the activity of specific regions or circuits by up- or downregulating MRI signals directly in their visual field. Thus, fMRI neurofeedback techniques have been used to downregulate amygdala response to adverse stimuli in normal subjects, thereby enhancing their emotional self-regulation (Sarkheil et al., 2014) upregulating amygdala response to pleasurable stimuli in depressed subjects suggesting the possibility of this treatment for anhedonia (Young et al., 2014).

A third level of genetic expression occurs entirely through the medium of social relationships. Heritable features of children evoke a broad range of responses from parents, siblings (Klahr & Burt, 2014; Pike, McGuire, Hetherington, Reiss, & Plomin, 1996; Reiss et al., 2000a), and peers (Manke, McGuire, Reiss, Hetherington, & Plomin, 1995; Rose, 2002), and heritable features of adults influence their level of perceived social support and exposure to stressful events (Kendler & Baker, 2007; Kendler & Karkowski-Shuman, 1997; Kendler et al., 1995). Findings such as these led Reiss et al. (2000c) and Kendler (2001) to propose that these genetic effects on environmental process constitute a major pathway of the expression of genetic influences on psychopathology. A number of longitudinal studies have supported this idea using twin (Burt, McGue, Krueger, & Iacono, 2005; Larsson, Viding, Rijdsdijk, & Plomin, 2008), adoption (Elam et al., 2014; Harold et al., 2013), and molecular methods (Propper, Shanahan, Russo, & Mills-Koonce, 2012). Kendler estimated that 16 % of the genetic influence on depression was expressed through genetic influences on

exposure to stressful life events and on social support (Kendler, 2001); Neiderhiser and her colleagues (2013) estimate that *all* of the genetic influence on initiation of illegal substance use in young adults was expressed through genetic influence on their families and peer selection when they were adolescents.

These “outside the skin (Kendler, 2001)” mechanisms of genetic expression are conspicuous but never used targets for psychosocial interventions to blunt the expression of genetic influences. In a recent paper already cited, Fearon and his colleagues (2014) showed that rearing parents’ marital satisfaction played a decisive role in the impact of their adopted children’s heritable characteristics on their experience of parenting. Fearon characterized young children’s liability for externalizing disorders by assessing birth parents’ psychopathology. Where marital satisfaction was low the rearing mother’s perception of her own parenting was negative, probably because the child was perceived as vexatious. However, in the context of a favorable marriage, mothers saw the child with the same genetic risk in positive terms and expressed positive parental feelings. The effect of marital dissatisfaction on the evoked maternal feelings played a notable role in the evolution of conduct and related problems in the developing toddlers. These findings suggested that early marital interventions might abort the expression of genetic influence on child psychopathology by *interrupting an unheralded but important pathway of gene expression*.

However, it is far from secret that early family interventions are effective in promoting positive child development preventing the evolution of child psychopathology (Cowan & Cowan, 2010). There is good evidence that focus such interventions on the parents marriage has additional yield. Does genetic information add anything to the mix already available? What would be possible now, to continue with the data provided by Fearon and his collaborators, is to deliver marriage-centered preventive intervention *within the context of a genetically informed design*. To what extent is the success of a marriage-oriented intervention dependent on blocking the “outside the skin” mechanisms of gene expression and to what extent is therapeutic success attributable to social mechanisms independent of the child’s genotype? For example, does marriage-oriented intervention eliminate the correlation of birth parent psychopathology with differences in behavior problems among children placed for adoption? What behaviors in the child or alternations in maternal perceptions are critical to this “anti-genetic” effect? What other outside the skin pathway might be blocked by such an intervention and might some of the positive outcomes be measured by child’s physical health?

Defining the Timing of Behavioral Interventions

There is increasing interest in integrating both quantitative and molecular genetics in the study of the life course. This has been aided by increasingly sophisticated, genetically informed conceptual analyses of the life course (see Shanahan & Hofer, 2011) as well as by extended longitudinal studies of twins, adoptees and longitudinal studies that have included both genotyping and assay of gene methylation or

expression. So far evidence has been brought forward to tackle three major developmental questions highly relevant to the timing of interventions.

The first use is to identify major developmental discontinuity, particularly periods when earlier influences on development rapidly fade away and new ones take over. The simplest strategy is to note, in longitudinal twin or adoption studies, the *balance over time between genetic and environmental influences* on a particular line of development. For example, the influence of environments shared by siblings, but differing among families, is the predominant influence on general intelligence from ages two to four but genetic differences among children play, by far, the major role from ages seven to ten (Davis, Haworth, & Plomin, 2009). Davis and colleagues suggest a simple explanation for this finding: variability among families in intelligence-promoting aspects of the environment may decrease owing to the uniformity of school curricula in the UK, the site of their study. However, their data suggests to the present author that variability in environment actually increases leaving the most likely explanation as an absolute and very sharp increase in genetic influence from early to middle childhood.

However, as Davis and his colleagues comment, there are two very different mechanisms, each of which could explain this sharp increase. The first is that children become dramatically more effective in eliciting reactions from their parents, teachers, and friends: heritable features of intelligence such as verbal ability may elicit responses from others—more attention in the classroom and more intellectual stimulation at home—that serve to amplify the child's intellectual abilities. This gene-driven positive amplification process receives some support from molecular genetic studies (Propper et al., 2012) and twin studies (Reiss et al., 2000c) and represents a potentially important outside the skin mechanism of gene expression. Both these studies suggest that heritable factors in the child that elicit negative parenting impair cognitive abilities. However, the Propper study focused on processes in early childhood and Reiss and colleagues on adolescence so neither provides a clear explanation for the dramatic discontinuity between ages four and seven. Davis and colleagues advance a parallel explanation: the increase in genetic influence on cortical thickening and myelination during a period approximating the period of discontinuity they identified. However, even without clear mechanistic explanations these longitudinal twin data have great relevance for behavioral interventions to enhance children's intellectual capacities: effective interventions, if they are designed to parallel or compensate for naturally occurring variation among children, are likely to be different for early and middle childhood.

A second contribution of genetics to the timing of interventions is to estimate when environmental influences that have been unstable and fluctuating become stable influences on development across time. These are influences most likely to account for sustained influence on differences among individuals in their adjustment. Quantitative genetics has become a particularly powerful tool here with the advent of large numbers of longitudinal twins studies and a smaller number of longitudinal adoption studies. The analysis proceeds in two steps. First, the variance accounting for stability in individual adjustments is parsed into genetic influences and into two great classes of environmental variance: environments that differ among families and

environments that differ among siblings in the same family. An example of the former is social class and the latter, differential treatment by parents. Then, these same techniques can be used to specify specific environmental factors, of the between- or within-family variety, that exert a causal influence independent of genotype. The logic and methods of this analysis have been fully explained and exemplified (Plomin, DeFries, Knopik, & Neiderhiser, 2013; Reiss et al., 2000a).

A good example is precise specification of the role of marital process in adult development. Briley and Tucker-Drob (2014) and Tucker-Drob and Briley (2014) gave recently reviewed all longitudinal twin and adoption studies to determine when sibling-specific environments become both sizable and stable influences on individual development for both cognitive and personality function.

Sibling-specific environments are important but unstable in early development but by early adulthood their stability is comparable to genetic influences. Why might these be the case?

A most likely contributor is the emerging role of marital status and marital satisfaction in adult life. Indeed, whether one is married or not has major implications for medical and behavioral health. While selection effects may have some role in this remarkable effect, epidemiological (Laub, Nagin, & Sampson, 1998) and genetic analyses (Burt et al., 2010) suggest that not only is marital status causal but that it is differences between siblings in marital status that is decisive for the effect of marriage on mental health. The same holds true for marital satisfaction that has been specifically tested for its effects on both depression and positive mental health (Spotts et al., 2004, 2005). Genetic studies of the *spouses* of twins provide additional insight. On a very broad range of characteristics spouses of identical twins are no more like each other than spouses of fraternal twins (Lykken & Tellegen, 1993; Zietsch, Verweij, Heath, & Martin, 2011) and the correlations for both identical and fraternal twins are quite low for most spousal measures suggesting not only that genes play no role in mate selection but neither do environments shared by siblings. Adults pick mates in part as reflections of their own prior life course *as it is contrasted with their siblings*, a life course that takes on even further uniqueness as consequence of the distinctive relationship spouses build (and some destroy) together.

Despite strong evidence for the use of marital therapy to treat problems of individual adjustment (for example, see Whisman et al., 2006), evidence that is unrelated to genetic inquiry, genetic data provide novel perspectives for further development of marital interventions. It is striking that genetic data is the most persuasive we have that across the span of ordinary human development the quality of marital relationships plays decisive effect on early child development while—at the same time—providing unique contributions to the psychological and medical health of the parents themselves.

A third contribution to the timing of intervention, provided by genetic inquiry, is the *definition of critical or sensitive periods in development*. While often clear in animal development (e.g., Hubel & Wiesel, 1970; Liu et al., 1997; Meaney, 2001), these periods are much harder to define in human development, particularly for complex behaviors. Animal models provide decisive data because researchers can control the “on” and “off” times of unfavorable or favorable environments. Thus Hubel and

Wiesel could suture one eye of a kitten and remove the suture at varying subsequent times in order to determine the critical period for the development of binocular vision. A similar quasi experiment is available in congenitally deaf humans who have hearing restored at various ages by cochlear implants.⁴ Other human designs permit estimates of “on” and “off” time boundaries for adverse or favorable environmental impact but genetically informed adoption studies provide the most decisive human data. Adoption at conception designs (contrasting mothers who have their own egg implanted versus mothers having eggs implanted from genetically unrelated donor) distinguishes between two possibilities. First, is an adverse influence such as smoking linked to a behavior outcome such as antisocial behavior because of genes shared by mother and fetus? In this case there would be a correlation between maternal smoking and child antisocial behavior only where the mother’s own egg was implanted. An exposure effect of smoking during pregnancy would require the same effect size for fetuses developing from a donated egg. Initial reports using this method suggest that smoking exposure leads to restricted fetal growth but not to antisocial behavior, thus pointing to genetic influences on the observed correlations (Rice et al., 2009). Adoption at birth designs distinguishes between prenatal and postnatal influences and even their interactions. For example, an adoption at birth study suggested that inconsistent parenting *postnatally* could influence a child’s cortisol levels when the fetus was exposed to a combination of maternal stress and drug use *prenatally* (Marceau et al., 2013). Finally adoption at varying intervals post birth, particularly for children subjected to harsh condition prior to adoption, allows an estimate of timing beyond which certain developmental achievements cannot be established despite favorable rearing in the adoptive home. For example, a distinctive form of “disinhibited attachment” (a child indiscriminately becomes attached to many different people) persists for years, despite variation in adoptive families, if the child is raised in an institutional setting for more than 2 years (in comparison to those adopted at 16 months or less). These data suggest that a critical period for forming more focused attachment is the latter half of the second year of life; after 2 years this focused attachment (secure or insecure) cannot be established.

Genetic Influences on Response to Treatment

Arnold Gesell’s experiments have long been forgotten and Fox’s publication has received only scattered citations. Only a single investigator has, in relation to that paper, used the twin method to explore the role of genetic influences on motor learning and on a task pairing muscle stimulation with transcranial magnetic stimulation

⁴In human development, considerable attention has been focused on hearing and language development because of the natural experiment of cochlear implantation that provides hearing to congenitally deaf children. While cochlear implants tend to be less effective over the age of 8, there is no sharp temporal breaking point and the age at which cochlear implants start to become less effective depends heavily on the nature of the auditory or perceptual test (Harrison, Gordon, & Mount, 2005).

and with muscle stimulation, a probe of neural plasticity (Missitzi et al., 2011, 2013). Thus, although Gesell and Fox were vanguards, they were entirely without influence on current efforts to use genetic techniques to explore individual differences in response to behavioral treatments. Even more pertinent to this historical discontinuity is the failure to use either the twin or adoption methods in exploring individual differences in response to behavioral interventions although clear proposals have been published (Plomin & Haworth, 2010; Reiss et al., 2000a). We will return to the essential role of these approaches.

The current impetus in this field comes from two sources. First, is the growing interest in measured gene by environment interaction on measures of adjustment across the life span. Investigators have focused on genes that, in interaction with the environment, have a plausible role in pathogenesis of behavioral disorders. They have hypothesized that these same genes may also play a role in differential response to treatment since treatment can be considered an experimentally controlled environmental variable. We have already reviewed an example in the work of Uhl and his colleagues for genes that are associated both with response to treatment and with enhanced risk for adolescents to become smokers. However, in this work findings on genetic influences on individual difference in response to treatment came first.

A particular incentive for research has been the theory of “differential susceptibility.” Originally articulated by Kendler and Eaves (1986), this theory posits that the behavioral effect of some alleles is to enhance children and adults’ susceptibility to environmental influence, for better or for worse. The first publication illustrating this principal, of which the writer is aware, was that of Lyman Wynne and his colleagues showing that children of mothers with schizophrenia and who were placed for adoption early in life had a *greater* chance than control children of developing thought disorder in a unfavorable rearing family but *less* of chance for disorder when raised in a favorable family setting (Wahlberg et al., 1997). Ten years later Jay Belsky revived this idea, apparently unaware of the work of Kendler and Wynne, and pointed to a number of measured gene x environment interaction studies that might support it (Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2007). A critical test of this theory would be to demonstrate that an allele that conferred risk for a behavioral disorder in children (or adults) subjected to an adverse environment would also serve to enhance the effect of a positive environment such as that provided in a randomized clinical trial.

However, beyond the theory of differential susceptibility, the large force stimulating work in this area is the enormous enthusiasm in the biomedical community for the prospects of “personalized medicine.” In this initiative we can recognize the same two aims we summarized for the genetics of behavioral intervention: defining new targets for treatment and better discrimination among patients between those who will respond to treatment and those who will not. Notable success, for example, has been achieved in breast cancer. Three advances in *distinguishing among breast biopsies* are now part of standard practice: the detection of progesterone and estrogen receptors that can be identified by tissue staining techniques and the detection of human epidermal growth factor (HER2), an assay that often uses genetic techniques (Giordano et al., 2014). Genetic analysis has also distinguished *among*

patients those that effectively metabolize tamoxifen, a drug indicated for estrogen receptor positive tumors, into its active metabolite. Good metabolizers can be identified before treatment by genotyping for a particular cytochrome enzyme. “Poor metabolizers” are generally not good candidates for tamoxifen treatment (Higgins & Stearns, 2011).

Identifying candidates for tamoxifen treatment is a good example of the value of “pharmacogenetics,” a technique that has been applied to many psychotropic drugs. Indeed, of over 170 drugs now required by the FDA to include genomic data on labeling instructions, as of January 2015 there are 24 psychotropic drugs listed, almost all of them are antipsychotic or antidepressant medications (<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>). However, in each instance, the required genetic data refers to the cytochrome system. This system, sited mainly in the liver, has been known for years but genotyping is an efficient way of ascertaining its properties and their influence on drug dosing and drug–drug interactions. No genomic labeling data required by the FDA reflects current advances either in neuroscience more generally or the genetics of brain function. However, there is a burgeoning literature that does take advantage of some of this knowledge, particularly about receptor systems in the brain (see Reynolds, McGowan, & Dalton, 2014 for a recent review). Reliable findings across studies are emerging. For example, in a meta-analysis of 15 studies of individual differences in response to SSRIs, Serretti, Kato, De Ronchi, and Kinoshita (2007) reported that the long form of the serotonin transporter gene enhanced response to treatment.⁵

The application of genetic techniques to analyze differences in patient response to standardized behavioral treatments (Reiss, 2010a, 2010b) has been the topic of considerable theoretical attention (Haworth & Davis, 2014; Plomin & Haworth, 2010; Reiss et al., 2000b). In principal, this approach can help improve the matching of particular treatments to particular individuals and even explore some of the mechanisms by which behavioral interventions might be effective; it can illumine the field of gene x environment interaction, and can place behavioral interventions within a broader study of developmental psychobiology.

The motivating vision of “personalized medicine” is to utilize insight from modern biology to better target treatments and select individuals who will respond to those treatments. We have reviewed in some detail the relative success of behavioral genetics in clarifying individuals at risk for behavioral disorders, mechanism of gene expression that may be feasible targets, and the timing in development when intervention may be most effective. Elsewhere in this volume researchers will report on ongoing efforts to use molecular genetic techniques to account for individual differences in response to treatment; we provide a brief introduction here.

Coining the term “therapygenetics” Thalia Eley with her colleague Kathryn Lester, reviewed 14 studies of measured gene x therapy interaction which, at that juncture in the field, yielded few impressive findings (Lester & Eley, 2013). For

⁵Since Belsky and others have argued that the short form of this gene confers susceptibility to both unfavorable and favorable environments, these pharmacogenetic effects would appear to weaken the theory of differential susceptibility.

example, six of nine studies of the moderating effect of the short allele of the serotonin transporter gene showed no effect. Some of the studies retrospectively genotyped already treated sample, and analyses simply omitted those not genotyped, thus infringing on the benefits of randomization. Some studies followed only treated patients (see a brief follow report) (Eley et al., 2014). While providing clues about the role of genotype, DNA methylation and even SNP-based heritability⁶, as influences on patient change this design, cannot distinguish between treatment effects and varying speeds of spontaneous remission.

At this early stage of “therapygenetics” preliminary reports are sufficiently promising to pursue more adequately powered studies. These may give clues to some of the biological mechanisms by which behavioral therapies reveal their effects. As noted elsewhere (Reiss, Leve, & Neiderhiser, 2013), genetic main effects are essential in understanding G x E interactions. What neural or cellular mechanisms do the genes regulate that account for the differential effects of allelic variation on differential response of patients to treatment? For example, the association of allelic variation in the serotonin gene with amygdale function once offered such a hope. Could the gene-influenced enhanced reactivity, highlighted in initial reports, account for the greater responsiveness of patients to the positive effects of treatment? Tamoxifen is a good example as the main effect on the cytochrome system of the gene that moderates its effect fully explains how this genotype moderates treatment response. We are some distance however from deploying genetics to develop biologically mechanistic explanations for the effect of behavioral interventions. A more immediate yield may be to determine whether the effect of a broad range of treatments is all moderated by the same allelic variation in the same gene or sets of genes. This would aid the search for common factors among effective therapies, a major issue in contemporary psychotherapy research. Finally genetics might explore other central issues in the psychotherapy. For example, characteristics of parents have substantial effects on outcome of children in treatment (e.g., Hoza et al., 2000). In a sufficiently powered sample exploring the parents’ genotype as a moderator of child treatment would underscore the importance of this effect. Indeed, some of the apparent effect of child genotype in preliminary studies supported by Eley and others may reflect, in part, parental genotype effects.

Genetically based studies of response to treatment can also aid the study of gene environment interaction more broadly. Standards for statically inferring genotype x environment interaction are clear but often honored in the breach. Investigators are usually aware of the need to control for the effect of the child genotype on the environment being studied since such an effect can perfectly mimic a genotype x environment interaction. Similarly, where the environment studied is shaped by a biological parent

⁶This analysis proceeds in the opposite form from that of a twin design. This procedure compares all possible pairs of individuals in a sample and asks whether their degree of phenotypic similarity is matched by a comparable overlap in genetic structure. Because SNPs do not contain all possible genetic information the estimates of heritability by this method are usually less than that of the twin method. The genes involved are not identified and significant SNP heritability may be obtained in circumstances where not even a single gene reaches a threshold for an effect on the phenotype under analysis.

or sibling the genes shared between these and the offspring under study, so-called passive gene-environment correlation, can also mimic gene x environment interaction but is much less frequently accounted for (see Kim-Cohen et al., 2006 for a delineation of the problem and its solution). A nearly intractable problem is the possibility that an unidentified gene evokes the environment under study. Thus an unidentified gene x identified gene interaction can, again, mimic a gene x environment interaction. All of these problems are obviated when the researcher controls environmental variation as in a randomized controlled trial. However, most treatments that are effective against serious psychological problems often induce many changes in environments experienced by children and by adults. Thus, simpler experiments that, for example, allow researcher to control stress levels (e.g., Way & Taylor, 2010, 2011) may be part of such an effort. As noted, genetic investigation of responses to treatment also provides a stringent test of the differential susceptibility hypothesis.

Finally, the promise of genetic studies of differences in response to treatment has the long-term promise of linking intervention studies to a more general science of developmental psychobiology. Recall our example from the work of George Uhl on a set of genes associated with response to smoking cessation trials; these same genes distinguish among adolescents who go on to smoke and those who don't clarify that biological processes that, in ordinary development, contribute to desistance from smoking also favor response to treatment.

A Few Ideas About the Future

It seems very unlikely that the current chapter will have an appreciable influence on the course of research at the intersection of behavioral interventions and genetic variation among individuals. The forces propelling some lines of research in this area are very powerful and those slowing research are equally so. Thus a more modest hope for a concluding statement here is that it might serve to round out a chapter meant as one of many guides to both readers and student researchers entering this field and perhaps to give emphasis to points made earlier but now rephrased in terms of both encouragement and caution.

As the present writer has outlined elsewhere (Reiss, 2016), the history of behavioral genetics, the quantitative inferences drawn from twin and adoption studies, is the polar opposite from molecular genetics. The former is heading for its 100th birthday (although its birthdate is subject to some dispute); its methods were slow to develop, its assumptions have been clarified and painfully examined across decades, and its results tend to be highly replicable. However, as this chapter has illustrated, its potential for identifying targets for intervention—along with the timing of when interventions might be most effective—is substantial. In contrast, the exact birthday of the widespread use of molecular genetic analyses can probably be dated to the hour if not the minute: Kary Mullis's presentation of the PCR method for amplifying specific DNA sequences in 1983. At that moment, biology was forever changed; the method (with a few critical tweaks from less acknowledged colleagues) was applied

worldwide and in less than a decade Mullis had his Nobel Prize, one of the most bitterly contentious ever awarded. Aided by large investments by private companies, current methods—direct outgrowths of the work of Mullis and colleagues—are becoming less and less expensive. Molecular genetics has given the behavioral sciences more generally, and behavioral interventions more particularly, a gift with more apparently alluring properties than any method in the entire history of research on human behavior. The measured polymorphism seems like a godsend in a field with complex causes, endless problems of distinguishing cause and effect, multiple methods purporting to measure the same construct, cultural effects on measurements and results, and problems with the validity of retrospective assessment. First, current dogma regards a person's genotype as a definitive "first cause": preceding but not caused by environmental exposure including participating in a clinical trial of behavioral intervention.⁷ Second, unlike any other variable in behavioral science, researchers can revisit old cohorts of research subjects, obtain their genotypes, and reason that their results are identical to those they would have obtained at the outset of their study. Third, with suitable safeguards, a polymorphism is a polymorphism whether it is measured in Mongolia or Manhattan. Finally, identifying a specific polymorphism offers the promise of integrating behavioral intervention with the biology of the brain, the immune system, and biological stress response systems.

Given the understandable allure of genotyping subjects enrolled in behavioral interventions, this approach hardly needs encouragement. Rather, it needs some thoughtful caution and more rigorous design and replication. The bulk of studies, in this genre, reported thus far are those where genotyping is completed after trials have been conducted and completed. Invariably, some subjects cannot be located or do not give consent. Results are reported anyway even though it is impossible to maintain the rigors of an intention-to-treat design. While results are intriguing, as noted, conspicuous failures to replicate (e.g., Lester et al., 2015) have not been weighted in recent, highly selected reviews (e.g., Bakermans-Kranenburg & Van IJzendoorn, 2015). Moreover, many published studies fail—with some exceptions (e.g., Schlomer et al., 2015)—to attend to the basic toilette of molecular genetic studies, most conspicuously the confounding effects of population stratification by allele frequency. Finally, readers and journal reviewers of these studies have no way of knowing how many polymorphisms were assayed by investigators, in any given study, and whether those that are published were selectively harvested cherries. The stakes are high and ethical issues preemptory: misused genetic studies might become a basis to dissuade patients from receiving therapies that seem to be contraindicated by their genotype.

With these problems in mind, it is entirely reasonable to propose that post hoc genotyping of subjects in completed trials is reaching the end of a useful exploratory phase.

⁷While it remains the case that the genotype is fixed at conception it can no longer be regarded as naïve to earlier experience. A range of studies, mostly in animals, suggests that parental and even grandparental experience leaves an inheritable residue of altered gene expression. See, for example, a particularly vivid example of the transmission of fear conditioning to a very specific odor in an F_0 generation of mice that is transmitted to the F_1 and F_2 generations through hypomethylation of a highly specific genetic locus in the DNA of sperm cells (Dias & Ressler, 2013).

Future studies of genetic moderation of behavioral therapies need to be prospective and adequately powered. Genotyping must be done in response to the best available evidence of the role of the genetic variants selected for study in biological processes highly likely to influence response to treatment. Moreover, the genetic variants selected for study must be entered before the trial, along with other aspects of the design, in the “lock box” of clinicaltrials.gov or similarly accessible public databases.

What then of the more senior but more ignored older sibling of molecular and genetics studies, the quantitative genetic inferences drawn from twin and adoption studies? Its imaginative originators—the graduate student Curtis Merriman, the dermatologist Herman Siemens, and the psychologist Barbara Stoddard Burks⁸—were not ever nor will they be household heroes, even in the homes of geneticists. However, as noted above, the potential contributions of these methods to targeting interventions and to their timing are very promising. Detailed speculation about why these remarkable resources remain unused is beyond the scope of this brief chapter. Surely, one remedial approach is enhanced accessibility. A mournful fact is that inferences and statistical models employed in the evaluation of twin data, and to a lesser extent for data from adoption studies, are difficult to grasp. The work of the present author and his colleagues are as good an example as any of the use of complex inferential models that defy ready understanding, even by mathematically competent readers (see, for example, Narusyte et al., 2011). The utility of twin and adoption methods as tools for strong inference about environmental effects, including those induced by therapeutic or preventive interventions, is rarely taught in research training programs. Further, authors in this field need to improve their presentation and explication of inferences and statistical models in their reports of results. Senior researchers, using these methods, have argued for the utility of conducting behavior trials with twin (Plomin & Haworth, 2010) and adoption (Reiss et al., 2000c) designs but scattered attempts to develop such programs have been of little interest to grant review committees.

Summary

Genetic inquiry has stimulated a strong interest in linking studies of behavioral intervention to an understanding of human psychological development across the life span. This synthesis now mirrors broader developments in biomedicine. Can genetics aid in identifying more accurately targets for intervention and better predict who will respond to those interventions?

Thus far, quantitative genetics—using twin and adoption methods—has made the most solid contributions in part because these methods can specify both genetic and environmental factors within these two broad domains. Molecular genetics has achieved some early success in identifying young people at risk for developing serious disorders later in life. It remains unclear whether that success improves on an accurate history of behavioral difficulties in first- and second-degree relatives. Rapid

⁸ See Reiss (2016) for a brief historical summaries of genetics and behavior.

developments in gene expression assays currently attract monumental interest and resources but enthusiasm for these techniques must be tempered by recognizing that gene expression is tissue specific. The use of genotyping and gene-expression profiling to distinguish responders from nonresponders has the same promise and obstacles as these techniques face in broader biomedicine. We need a better understanding of both psychopathology and of mechanisms of action of interventions to make most effective use of these techniques. Or to put the matter another way these techniques provide useful data only insofar as they aid in that understanding. Research on tamoxifen, and similar drugs, where both mechanism of disease and drug action and metabolism are better understood, is a limited but important standard for behavioral research. However, unlike tamoxifen, the influence there is overwhelming evidence that the efficacy of behavioral interventions is shaped in good measure by social factors such as patient-therapist relationships, the marital quality of adults in treatment and parental attitudes of children in treatment. Data suggest this is likely to be true for pharmacotherapy as well. Progress in this field is unimaginable without equal attention to genetic and social determinants of treatment efficacy and how these two interact. Here twin and adoption methods become essential.

The role of twin and adoption studies in understanding the difference between responders and nonresponders to standardized behavioral interventions is tragically underutilized and this under use seriously retards progress in the field. These are powerful techniques for clarifying both environmental and genetic contributions to differential response to interventions and to identifying what these factors might be. Because of the immense cost of sample accrual, they are impractical for individuals already suffering major disorders. For example, to study environmental and genetic effects on the treatment of childhood anxiety we would require a sample of twins all of whom suffered child anxiety disorders. However, these techniques could be deployed brilliantly in the study of preventive intervention in high-risk twin samples. Such samples have been accrued and yield enormous insight into the interplay of genetic factors and the environment. By their nature, prospective adoption studies contain high-risk children because, in the USA at least, birth parents who place their children for adoption at birth have high prevalence of behavioral and substance abuse disorders. Indeed, the integration of quantitative and molecular genetic investigation is nowhere more important than in linking behavioral intervention to an understanding of human development.

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