Exploring the gene–environment nexus in eating disorders

Cynthia M. Bulik, PhD

Department of Psychiatry, School of Medicine, and Department of Nutrition, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Early theories of eating disorders focused on aversive family and sociocultural factors as fundamental to the development of these problems. A progression of family, twin and molecular genetic studies has demonstrated a substantial role for genetic factors in the development of anorexia nervosa, bulimia nervosa and related traits. Paradoxically, genetic studies hold promise for refining and enriching our approach to understanding the impact of adverse environmental forces. The development of new and more sophisticated approaches for understanding the complex interplay of genetic and environmental effects will allow enhanced understanding of both risk and protective environmental factors and how they may influence expressions of underlying genetic vulnerabilities to eating disorders.

Les premières théories sur les troubles de l'alimentation portaient avant tout sur des facteurs familiaux et socioculturels aversifs qui jouaient un rôle fondamental dans l'apparition de ces problèmes. L'évolution des études sur la famille, les jumeaux et la génétique moléculaire a démontré que des facteurs génétiques jouent un rôle important dans l'apparition de l'anorexie mentale, de la boulimie et de caractéristiques apparentées. Les études de génétique promettent d'améliorer et d'enrichir notre façon de comprendre l'incidence des forces environnementales indésirables, ce qui est paradoxal. La mise au point de stratégies nouvelles et plus sophistiquées pour comprendre l'interdépendance complexe entre les effets de la génétique et ceux de l'environnement permettra de mieux comprendre les facteurs à la fois de risque et de protection de l'environnement et comment ils peuvent jouer sur les vulnérabilités génétiques sous-jacentes qui s'expriment sous forme de troubles de l'alimentation.

Introduction

For decades, if not centuries, society[1] and the family[2,3] have been held responsible for eating disorders. Although there is no doubt that both of these environmental factors influence the development of eating disorders, they do not on their own cause these disorders. Such a simplistic approach to eating disorders is an excellent example of the pitfalls of face validity, whereby it has been easy for clinicians and researchers to believe what appeared to be an obvious explanation for the puzzling phenomenon of anorexia nervosa. Unfortunately, the trap of face validity greatly undermined efforts both to understand the neurobiology of eating disorders and to develop effective treatments for these often intractable illnesses.

How have things changed over the past few decades? Briefly, family studies have demonstrated the familial aggregation of eating disorders and related traits.[4,5] This observation has been further elucidated by a series of twin studies, which have clarified that the familial aggregation is largely influenced by additive genetic effects.[6–9] Finally, the past decade has seen a virtual explosion of association and linkage studies of anorexia and bulimia nervosa that are beginning to identify genomic regions and candidate genes that may be implicated in the risk for these disorders (see Hinney et al[10] and Bulik and Tozzi[11] for reviews).

In addition to invigorating neurobiologic research about eating disorders, this body of genetic research has paradoxically opened up the potential for greater specificity in our understanding of the role of environment. Rather than relying

Correspondence to: Dr. Cynthia M. Bulik, Department of Psychiatry, University of North Carolina at Chapel Hill, 1st floor Neurosciences Hospital, 101 Manning Dr., CB #7160, Chapel Hill NC 27599-7160; fax 919 966-5628; cbulik@med.unc.edu

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on nonspecific blanket theories related to a universal exposure such as the presentation of thin ideals in the media, researchers may soon understand the genetic variants that make some individuals more vulnerable than others to environmental insults such as strict dieting prompted by exposure to extreme media ideals. Ultimately, this work has led researchers to re-evaluate their understanding of how the environment exerts its influence on people who are genetically vulnerable to eating disorders and is forcing the development of new models to explain how genes and environment interact to influence this vulnerability.

The role of genetics

Family and twin studies

Patients with eating disorders have consistently reported the presence of either frank eating disorders or suggestive traits in family members. Most commonly, the clinician hears of a relative who ate exceedingly sparingly or had quirky eating behaviours. Although perhaps unnamed and undetected, such behaviours often suggest a threshold or subthreshold eating disorder that may be discerned by further inquiry. Formal family studies of both anorexia nervosa and bulimia nervosa have shown that these disorders are substantially familial. Relatives of patients with eating disorders have approximately a 10-fold greater lifetime risk of such disorders than relatives of unaffected people.[4,5,12–14] Moreover, mirroring the common clinical observation of diagnostic crossover,[15] family studies indicate that these disorders do not "breed true": relatives of people with anorexia nervosa may themselves have a more bulimic clinical presentation and vice versa.[4,5]

Further insight into familial transmission has been provided by twin studies, which, unlike family studies, allow the researcher to parse out sources of familial aggregation, at least to some extent. Variance in susceptibility to eating disorders can be partitioned into additive genetic, shared environmental and unique environmental factors. Eating disorders are complex traits, and additive genetic effects are the cumulative effects of many genes, each of which has a small to moderate effect. Shared environmental factors contribute to the similarity of twins and reflect environmental influences to which both members of a twin pair are exposed. Finally, unique environmental factors, which include error of measurement, refer to environmental forces to which only one member of a twin pair is exposed. With this information, heritability can then be calculated; however, any heritability estimate is a product of trait prevalence, monozygotic twin concordance and dizygotic twin concordance and is specific to a given population at a particular point in time. As such, there is no single definitive heritability estimate for anorexia nervosa. The influence of changing prevalence on heritability was nicely illustrated by Kendler et al,[16] who compared the heritability of tobacco use in Sweden between 2 historical cohorts — one in which smoking was relatively rare among women and the other in which smoking had become more prevalent throughout society. The heritability of tobacco use in men in these 2 cohorts remained similar over time (about 63%) (as did prevalence, since there were no prohibitions against men smoking). In contrast, the heritability of tobacco use in women jumped from near 0% to 63%. These results illustrate the importance of a deep understanding of the factors that influence any heritability estimate and the context in which it is measured.

Several twin studies of eating disorders and related traits have now been conducted in many countries around the world, including the United States, the United Kingdom, Australia, Norway, Sweden, Finland and Denmark. These studies have consistently revealed moderate contributions of the additive effects of genes.[6,7,9,17–19] Heritability estimates have ranged from 33% to 84% for anorexia nervosa,[8,19–21] between 28% and 83% for bulimia nervosa (reviewed by Bulik and Tozzi[11]) and 41% (confidence interval 31%–50%) for binge-eating in the absence of compensatory behaviours (a proxy for binge-eating disorder),[22] with the remaining variance (in each disorder) attributable to individual specific environmental factors and negligible impact of shared environmental factors. Most of these estimates have been fairly imprecise as reflected in the broad confidence intervals. Nonetheless, consistent replication across samples and across countries, despite different assessment and diagnostic strategies, supports the observation that there is indeed some critical genetic component influencing risk for these disorders.

Moreover, certain assumptions, such as the equal environment assumption, must be met in twin studies to avoid bias in the derived estimates. The equal environment assumption posits that monozygotic twins are not treated more similarly than dizygotic twins on factors of causative relevance to the disorder. For example, although monozygotic twins might be dressed alike more frequently than dizygotic twins, dressing alike is unlikely to be a factor of major causative relevance to eating disorders. To date, no such gross violations have been observed, which lends further credence to the observed results.[9,23,24] It is critical that all of the twin studies of eating disorders have been conducted in primarily European populations. Little is known about the heritability of these disorders and traits in other cultures and ethnic groups.

Association and linkage studies

With a plethora of studies now emerging, several reviews of the molecular genetics of eating disorders have been published.[10,11,25] Both association studies, which compare people displaying a trait of interest with controls who do not display the trait and then determine the genotypes of all subjects for a candidate gene or genes hypothesized to be of relevance to the phenotype, and linkage studies, which require a large sample of multiplex pedigrees or extreme sibling pairs,[26] have been conducted for eating disorders.

The corpus of association studies reveals occasionally significant but often unreplicated findings. Because of the role of serotonin in feeding and mood, genes in the serotonergic system have received particular attention. Associations have been observed with the serotonin receptors 2A[27–31] and 2C,[32,33] as well as the serotonin transporter gene,[34,35] although replication of results has not been universal.[36–43]

Steiger et al[44] examined factors associated with the promoter region of the serotonin transporter gene (*5-HTTPLR*) in women with "binge–purge syndromes" (which included bulimia nervosa, eating disorder not otherwise specified and anorexia nervosa bingeing-purging subtype). Although the *S* allele was not associated with eating disorder symptoms or related traits, it *was* associated with borderline personality disorder and impulsive traits. Moreover, the presence of the *S* allele was associated with a significantly lower density of paroxetine binding sites, which suggests that these patients might not respond as well to traditional selective serotonin reuptake inhibitors. Steiger et al hypothesized that differences in paroxetine binding might be due to an interaction of environmental and genetic factors, given that chronic food restriction in animals is associated with serotonin dysregulation. That study highlighted the importance of measuring specific traits associated with eating disorders and the potential richness of exploring gene–environment interactions that may affect therapeutic response.

Other systems of interest in the development of eating disorders include norepinephrine[45,46] and estrogen[45–47] genes. Although these studies have not been universally replicated, patterns are emerging in the literature on the genetics of eating disorders. Ultimately, these genetic investigations could lead to further elucidation of the neurobiologic pathways implicated in eating disorders and might reveal rational drug targets.

Linkage studies for both anorexia nervosa and bulimia nervosa[48–52] have underscored the importance of looking beyond the diagnoses of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,[53] that have been identified in genetic studies and seeking reliable endophenotypic traits that might bring us closer to the core neuropathology of these disorders. Focusing on the most homogenous presentation of anorexia nervosa — the classic restricting subtype of anorexia nervosa in the absence of binge-eating behaviour — yielded evidence for a susceptibility locus on chromosome 1.[50] Further analyses of this data set led to the incorporation of behavioural covariates into linkage analyses. Devlin et al[49] selected and incorporated core behavioural covariates (drive for thinness and obsessionality) into the linkage analysis. The inclusion of these covariates revealed several regions of interest on chromosomes 1, 2 and 13. This team has also explored the regions under the linkage peaks for association.[54] Both serotonin 1D (*HTR1D*) and delta opioid (*OPRD1*) receptor genes exhibited significant association with anorexia nervosa. The only published linkage study of bulimia nervosa[51] reported significant linkage on chromosome arm 10p for a broad sample of families with this condition.

Although genetic research has catapulted the field into a new era, genes paint only part of the picture. The identification of genes that influence risk for eating disorders does not mean that attempts to reduce noxious environmental exposures, such as unrealistic expectations about physical appearance and slenderness, should be eased. Yet how can genetic research help in identifying which individuals might be differentially vulnerable to these environmental insults?

The role of the environment

There are several ways in which genes and environment can interact. The most familiar is the gene–environment interaction, whereby a person's genes may influence how sensitive he or she is to the effects of the environment.[55,56] This interaction is particularly relevant in the study of eating disorders, given the nearly ubiquitous exposure of young girls in Western society to ideals of slenderness. Historical sociocultural theories of eating disorders were unable to explain why, if all young girls are exposed to cultural standards of thinness and attractiveness, only a small number ever experience eating disorders. The gene–environment interaction is a potential explanatory model. According to this model, individuals are differentially vulnerable to an insult such as strict dieting because of differences in their genotypes; this differential vulnerability could then be the first step in the development of anorexia nervosa. For example, those with lesser genetic loading for this vulnerability might see slender models, try dieting, find it an aversive experience and return to normal eating. In contrast, those with a greater genetic vulnerability might find dieting to be particularly reinforcing — either by reducing negative or dysphoric affect or by providing a sense of control or accomplishment. These individuals, with their particular genotype and biologic and psychologic responses to dieting, would be at greater risk for anorexia nervosa.

Cycle of risk: Gene–environment nexus?

Unfortunately, unpacking the interplay of gene and environment is challenging. With certain novel study designs and special patient samples, however, it may be possible to model the manner in which genes and environment mutually affect each other to influence risk. One recently developed hypothesis[57] suggests a mechanism whereby anorexia may be perpetuated across generations. This is particularly relevant today, as clinicians are reporting greater numbers of patients presenting for treatment in midlife. This hypothesis unites population-based data on the risk factors for anorexia nervosa with clinical data regarding pregnancy outcome in women with a history of eating disorders.

First, population-based studies have shown that the risk of anorexia nervosa is approximately 3.6 times greater in people who were born prematurely, especially if they were small for gestational age,[58] and that this effect remains even with adjustment for relevant sociodemographic factors.[59] Moreover, clinical and population-based studies of pregnancy outcome in women with current or past anorexia nervosa indicate greater risk of infants with low birth weight, prematurity, perinatal death, congenital abnormalities and other obstetric complications.[60–65] Both animal and human studies indicate that these outcomes are consistent with maternal undernutrition during the gestational period.

It is conceivable that a genetic tendency toward anorexia nervosa may render it exceedingly difficult for women with a history of this disorder to achieve adequate weight gain during pregnancy. Although they are perhaps not grossly undernourished, their diet might nonetheless be inadequate to sus-

tain a healthy pregnancy. This in turn could lead to the outcome of small or premature babies, which itself might represent a risk factor for later development of anorexia nervosa in the offspring. Thus, what on the surface could be labelled an environmental factor (inadequate nutrition and weight gain during pregnancy) may actually be influenced by genetic factors (maternal predisposition to eating disorders leading to inadequate pregnancy weight gain). If, as has been shown, women with anorexia nervosa also have difficulty maintaining breast-feeding and providing a nurturing feeding environment for their children,[64] despite their deep desire to parent effectively, the offspring may be dually challenged by a genetic predisposition to eating disorders and exposure to an environment in which food and eating are affectively charged and laden with anxiety (i.e., a gene–environment correlation).

Progress in this area requires studies of large samples of people for whom both genetic and environmental measures are available. Several such data sets exist around the world and their use should be optimized to help in understanding how these powerful forces interact to influence risk for eating disorders.

Conclusions

A comprehensive understanding of the causes of eating disorders must take into account genetic and environmental factors and their interplay. Although viewed skeptically by some, genetic research is opening new frontiers in research on the role of environment. Close collaboration between researchers knowledgeable about the genetics of eating disorders and those able to assist with optimal measurement of environmental factors are essential for progress. Such progress will depend not only on the merging of these areas but also on the development of novel methods and analytic approaches to capturing the complex gene–environment nexus.

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