Exploring the Gene-Environment Nexus in Anorexia, Bulimia

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Although eating disorders have been considered to be largely sociocultural in origin, findings from family, twin and molecular genetic studies conducted during the last decade are refuting that perspective. Recent studies have had significant success in isolating specific chromosome regions that may harbor susceptibility loci for anorexia and bulimia nervosa and are helping to shed light on the degree of heritability of eating disorders.

Although eating disorders have been considered to be largely sociocultural in origin, findings from family, twin and molecular genetic studies conducted during the last decade are refuting that perspective, an expert in genetic epidemiology told attendees at the recent 2nd World Congress on Women's Mental Health in Washington, D.C. (Bulik et al., 2004).

"Twenty years ago when I started in this field, and gave my favorite lecture on eating disorders, it was all about the role of the family and social factors in the etiology of eating disorders," said Cynthia M. Bulik, Ph.D., William R. and Jeanne H. Jordan Distinguished Professor of Eating Disorders in the department of psychiatry and director of the eating disorders program at the University of North Carolina, Chapel Hill. "Both anorexia and bulimia were very much viewed as disorders of choice. These young girls were viewed as trying to emulate some cultural ideal and diet themselves down to a certain weight. Now, any patient would have told you had you listened that wasn't what they were doing. They went far beyond any societal ideal in Cosmopolitan or any other magazine."

Bulik explained that when she and colleagues started talking about genes as being involved in these disorders, "people pretty much thought we were out of our minds." However, the investigators are discovering a complex interplay between genes and the environment leading to the development of anorexia nervosa (AN) and bulimia nervosa (BN).

"Anorexia nervosa has the highest mortality rate of any psychiatric disorder, with the most common causes of death being secondary to starvation and suicide," said Bulik, who is immediate past-president of the Academy for Eating Disorders. The mortality rate at five years is 5%, increasing to 20% at 20-year follow-up (American Psychiatric Association Work Group on Eating Disorders, 2000).

Anorexia nervosa is estimated to affect between 0.5% and 1% of U.S. women and girls. Symptoms and identifying characteristics of AN can be found in the Table. Most commonly, the onset is around puberty, although clinicians are seeing more prepubertal-onset cases. There is also a rise in midlife-onset cases.

"Some of these people are women who had eating disorders or anorexia in their teens and had a period of recovery and then developed it again in midlife. We are also seeing interesting cases of new onset in midlife," Bulik said.

Bulimia nervosa affects 1% to 2% of adolescent and young adult U.S. women. Symptoms and characteristics of the disorder can be found in the Table. "It occurs at all body weights, so you can't tell if someone has bulimia nervosa just by looking at them," she said.

Bulik noted that there is a female preponderance in bulimia, but the diagnostic criteria are "basically an accepted set of female norms."

"We need to look at the ways men experience body dissatisfaction and to focus on the methods men use to change their bodies," she said. "They [men] usually focus on increasing their lean mass or becoming more muscular."

Bulik continued with a brief description of genetic epidemiology, which looks at how genes and environment influence the risk for specific disorders. The first question asked is whether eating disorders run in families. If the answer to the family studies is that the disorder does run in families, the next step is twin and adoption studies to help determine the extent to which the disorder is due to genes or the environment. If genes are determined to be important, the researchers move on to conducting linkage and association studies to identify where the genes are and what they do. Both AN and BN are strongly familial and are, in fact, as familial as schizophrenia and bipolar disorder, Bulik said.

"They don't breed true, in that a patient with anorexia doesn't only have family members with
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anorexia. You will see a mixture of eating disorders among the family members—bulimia, eating disorders [not otherwise specified] and threshold eating disorder behaviors. But relatives of individuals with eating disorders are at seven to 12 times higher risk than relatives of individuals without eating disorders. The familiality of anorexia nervosa is the highest; they tend to have the densest family history," she said.

While there are no published adoption studies for AN or BN, Bulik said, twin studies do exist. In twin studies, researchers compare concordance rates (the frequency with which both members of the twin pair have the disorder or the trait of interest). They compare those concordance rates in monozygotic and dizygotic twins.

Bulik explained that eating disorders are complex, and investigators know they are looking for multiple genes and environmental factors. To do that, the investigators are going beyond concordance rates in twins and looking at three different pockets of variance: the additive effect of genes; shared environmental effects, such as family religion, parental rearing style or socioeconomic status in which the twin pair was raised; and unique environmental effects, those things that happen in the environment that will influence one of the twins but not the other. For example, one of the twins joins a gymnastic club where an incompetent coach pressures her to diet to an unrealistic weight, while the other twin joins a soccer team where weight is not a major issue.

"When we started to do twin studies, we were all surprised, given that we had all grown up in that sociocultural tradition of eating disorders. When we look at those three pockets of variance, we actually find that the heritability of bulimia nervosa, for example, is somewhere between 59% and 83%. So what we are saying is the liability for developing bulimia nervosa is predominately affected by genetic factors. Shared environment wasn't terribly important. The remainder of risk comes out in those unique environmental factors—those slings and arrows of outrageous fortune," Bulik said.

"Similar results came for anorexia nervosa—with the heritability of 58% to 76%. Again, shared environment wasn't terribly important, and the unique environment seemed to influence risk for anorexia nervosa."

Several population-based twin studies conducted around the world, primarily on individuals with European ancestry, have similarly concluded that AN and BN, as well as related phenotypes such as perfectionism, body dissatisfaction and drive for thinness, are moderately heritable, Bulik indicated. A series of multisite studies supported by the Price Foundation of Geneva have helped identify possible areas on chromosome 1 for AN and areas on chromosome 10 for BN that may harbor susceptibility loci for these disorders.

Bulik described some of the studies in which she was an investigator, along with many others. Others involved in managing the genetic data were Walter Kaye, M.D., professor of psychiatry at the University of Pittsburgh School of Medicine; Bernie Devlin, Ph.D., associate professor of psychiatry at the University of Pittsburgh School of Medicine; Wade Berrettini, M.D. Ph.D., professor of psychiatry at the University of Pennsylvania School of Medicine; and Andrew Bergen, Ph.D., senior scientist at the Advanced Technology Center of the National Cancer Institute.

"The first study we did involved 192 individuals with anorexia nervosa and their affected relatives," said Bulik. "The probands had anorexia nervosa, but the family members could have had a whole cluster of eating disorder diagnoses. The results were underwhelming. So we decided to look at what would be the core phenotype for anorexia nervosa to clarify our analysis." The investigators performed a linkage analysis in a subset (n=37) of families in which at least two affected relatives had diagnoses of restricting AN, a subtype characterized by severe limitation of food intake without the presence of binge-eating or purging behavior. By doing so, the investigators observed that the highest nonparametric linkage (NPL) score was 3.03 at marker D1S3721 on chromosome 1p (Grice et al., 2002).

"Subsequently, we found two genes under that peak—one related to the serotonergic system and one related to opioidergic system that may influence risk for anorexia nervosa," Bulik said. A second study funded by the Price Foundation looked at bulimia and involved two linkage analyses (Bulik et al., 2003). To identify regions of the genome harboring genetic variants conferring susceptibility to BN, the investigators conducted a linkage analysis of multiplex families with eating disorders who were identified through a proband with BN. Linkage analysis of the entire sample of 308 families yielded a double peak, with the highest nonparametric multipoint maximum LOD score (MLS) of 2.92 on chromosome 10.

The investigators then sought to analyze families who showed noteworthy elevation in vomiting behavior, for which other studies had found a substantial heritability. Consequently, the investigators then performed linkage analysis in a subset of 133 of families in which at least two affected relatives reported a symptom pattern that included self-induced vomiting. The highest MLS score observed...
(3.39) was on chromosome 10, between markers D10S1430 and D10S1423, thus providing evidence of the presence of a susceptibility locus for BN on chromosome 10p. While the focus on vomiting behavior may sound strange, Bulik explained that part of the game in doing genetic studies is to define your phenotype as clearly as possible. The human genome is a huge place, with an estimated 40,000 genes. It is hard to know where to look for genes.

To narrow the search, investigators look at a particular region and look closely for candidate genes that may be of relevance to a phenotype. The human genome is highly unlikely to map onto our diagnostic categories; it is just not going to be that simple. We won't find the anorexia gene or the bulimia gene," she said. More likely, the investigators are looking for genes that may influence proteins that may influence perfectionism, harm avoidance, appetite regulation, ease of vomiting, anxiety (a common premorbid condition in people with eating disorders), obsessialonality, high activity, obesity risk and binge eating, Bulik added.

"To complicate matters, we may have protective alleles, traits that protect against the expression of these risk alleles, like genes that influence self-esteem or genes that influence constitutional fitness. A couple of studies we have done show that individuals who tended to be thin all their lives are at much lower risk for eating disorders," she said. "Then you throw environmental factors in the mix, including protective factors such as breast-feeding. Unpacking the complexity of all these genetic and environmental factors is quite a task and also quite a challenge."

Once the investigators find the genes, they can use that information to better understand how the genes and environment interact. Bulik gave as an example a study by Caspi et al. (2003) that found an individual's response to environmental insults is moderated by their genetic makeup. In that study, a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression and suicidality in relation to stressful life events than individuals homozygous for the long allele. A similar process may hold true for eating disorders, said Bulik.

"To pull this all together, we need to look beyond nature versus nurture and pay greater attention to gene-environment interplay. Genetics research really enhances our ability to understand the role of environment," Bulik added.

She went on to discuss a new study she and colleagues are starting that builds upon findings from other studies. Some of the findings came from a Swedish study in which investigators used prospectively collected data about pregnancy and perinatal factors to examine the subsequent development of AN (Cnattingius et al., 1999). This population-based, case-control study was nested in cohorts defined by all live-born girls in Sweden from 1973 to 1984. Data from the Swedish Inpatient Register showed that 781 girls, ages 10 to 21, had been discharged from hospitals in Sweden with a main diagnosis of AN. For each case, five controls were randomly selected, individually matched by year and hospital of birth (n=3905). For girls, cephalhematoma (OR, 2.4; 95% CI, 1.4-4.1) and very preterm birth (lesser than or equal to 32 completed gestational weeks) (OR, 3.2; 95% CI, 1.6-6.2) were both associated with increased risk of AN. In very preterm births, girls who were small for gestational age faced higher risks (OR, 5.7; 95% CI, 1.1-28.7) than girls with higher birth weight for gestational age (OR, 2.7; 95% CI, 1.2-5.8).

Other studies have shown, Bulik said, that women with AN, even those who are recovered, continue to maintain a relatively low body weight, their body mass index (BMI) hovering somewhere about a mean of 19.

"Weight gain during pregnancy for these women is difficult and often inadequate. Pregnancy outcome for these women with anorexia nervosa includes preterm birth, low birth weight, prematurity, stillbirths, low Apgar scores and increased rates of cesarean [Goldman and Koren, 2003]," Bulik said. "The outcomes we are seeing in women with anorexia nervosa and a history of anorexia nervosa are consistent with maternal undernutrition in both animal and human studies, making us wonder if these women are malnourished throughout the course of their pregnancies. "So what we are hypothesizing is a cycle of risk, wherein a mother with anorexia nervosa fails to maintain adequate nutrition throughout her pregnancy, which increases her risk for labor and delivery complications, prematurity and babies who were small for their gestational age. Those factors, themselves, increase the risk of developing anorexia nervosa later in life, so we have a nasty cycle that can perpetuate itself across generations."
Bulik said she and colleagues are planning to start a study in Norway looking at 100,000 births and the risk of eating disorders. "We have extensive nutritional data on the women. We also have fetal ultrasounds, so we can look at growth in utero, and we have pregnancy outcome variables. The children are going to be followed up throughout adulthood, so we are going to be able to look at them through the ages where they are at risk for developing the disorder. But we can also go back and look at the maternal birth records of the moms, to see how many of the babies were premature, small for their gestational age, or other sorts of problems with labor and delivery. It will enable us to explore the cycle of risk across two generations in 100,000 births," she said. "So we are saying that perinatal events are not exclusively environmental, a genetic tendency toward anorexia may influence inadequate weight gain during pregnancy. It also underscores the importance of prenatal monitoring in pregnant women with current or past eating disorders in order to interrupt the cycle of risk."

The Norwegian study, Bulik added, "might really help us unravel that nexus where genes and environment collide."

(The National Institute of Mental Health is sponsoring a multicenter, international study seeking to determine whether a gene or genes might predispose individuals to develop AN. They need families with at least two members who have or had AN and who would be willing to participate. The study involves the completion of interviews, questionnaires and a blood draw. Participants do not need to travel and will be paid upon completion of the study. For more information call [888]895-3886, e-mail EdResearch@msx.upmc.edu or visit the Web site at www.angenetics.org--Ed.)

References: References

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