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Updates on Genome-Wide Association Findings in Eating Disorders and Future Application to Precision Medicine

Lauren Breithaupt[1,2], Christopher Hübel[1,3] Cynthia M. Bulik[1,4,5,*]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden [2]Department of Psychology, George Mason University, Fairfax, VA, USA [3]MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom [4]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [5]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA


Cynthia M Bulik

Abstract: *Heterogeneity, frequent diagnostic fluctuation across presentations, and global concerns with the absence of effective treatments all encourage science that moves the field toward individualized or precision medicine in eating disorders. We review recent advances in psychiatric genetics focusing on genome-wide association studies (GWAS) in eating disorders. Given that the only eating disorder to be the subject of GWAS to date is anorexia nervosa, we review anorexia GWAS and enumerate the prospects and challenges of a genomics-driven approach towards personalized intervention in eating disorders.*

Keywords: eating disorders, genetics, GWAS, heterogeneity, anorexia nervosa, polygenic risk score, heritability, pathways.

1. INTRODUCTION

Clinicians' options for the treatment of eating disorders — especially anorexia nervosa—remain meager at best. To date, only two medications (approved by the US Food and Drug Administration) are available that significantly improve the core symptoms of eating disorders in the short term (fluoxetine for bulimia nervosa [BN] [1], lisdexamfetamine for binge-eating disorder [BED] [2,3]). Evidence-based psychological interventions remain the recommended first-line approach to eating disorder treatment [4]. However, a subset of patients do not opt for psychological interventions, and those who do, in many parts of the world, do not receive evidence-based treatments [5]. The recent Diagnostic and Statistical Manual (DSM-5) [6] reclassification of feeding and eating disorders increased the number of young people meeting diagnostic criteria for eating disorders [7] and may also have increased heterogeneity both within and between diagnoses [8]. Recognition of the phenotypic and etiological variability within psychiatry has promoted a call for a precision medicine approach in the field [9–11], which may prove beneficial for eating disorders. Understanding the genetics of eating disorders has emerged as an important early first step in the quest for a precision medicine approach [9]. However, caution is warranted, as premature conclusions can cloud rather than clarify. We discuss the current state of genetics in eating disorders, focusing on genome-wide studies of DNA variation and their future role in precision medicine for eating disorders. Table **1** presents a broad overview of genetic methodologies previously used in eating disorders and current status.

*Address correspondence to this author at the Department of Psychiatry, University of North Carolina at Chapel Hill, CB #7160, 101 Manning Drive, Chapel Hill, NC 27599-7160, USA; e-mail: cbulik@med.unc.edu

2. GENETICS OF EATING DISORDERS

Early family studies and large twin-based studies of eating disorders formed the foundation of the genetics of eating disorders. Heritability estimates from twin studies continue to be one of the most consistently replicated findings within eating disorder pathogenesis [12]. Average heritability estimates across anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) range from 40% to 65% [13]. Limited research on the genetics of newly introduced purging disorder (PD) indicate familial effects, but replication is required [14,15]. Very little research exists on the heritability of night eating syndrome (NES), but the few studies indicate moderate heritability [16]. To date, no studies on the genetics of avoidant-restrictive food intake disorder (ARFID), pica and rumination disorder have been completed.

Initial linkage and candidate gene studies yielded inconsistent and ultimately unfruitful findings. Retrospectively, given the genetic architecture of psychiatric disorders, the linkage- and candidate-based approaches were unlikely to crack the genetic code to eating disorders. Linkage-based studies require costly large family pedigrees and candidate gene-based studies required much larger sample sizes and effect sizes than we ever imagined [17]. Moreover, in the absence of sound information about the underlying biology of the illnesses, candidate gene approaches rested on guess work regarding which genes might be operative. This is an unlikely goal as current estimates suggest that hundreds, if not thousands of genes will contribute to complex psychiatric phenotypes such as eating disorders [12,13,18,19]. In contrast, large-scale genome-wide association studies (GWAS) have historically provided much

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Table 1. Overview of genetic methodologies used in eating disorder research to identify genetic variants to date.

Methodologies	Type	Aim	Status
Quantitative Genetics	Family studies	Determine whether traits or disorders aggregate in families.	AN, BN, BED, PD runs in families.
	Twin & adoption studies	Estimate the influence and relative contribution of genetic and environmental factors on human traits. Distinguish between shared and nonshared environmental factors. Generate estimates of heritability.	Consistently demonstrate heritability and significant contribution of nonshared environmental factors in AN, BN, and BED.
Molecular Genetics	Linkage studies	Identifies genomic regions that have an increased likelihood of containing genes that are associated with a disorder or trait. Conducted on samples of related individuals (i.e., affected relative pairs, dense pedigrees) and does not require a priori hypotheses based on biological function or prior data.	Inconsistent results and few replications.
	Candidate gene association studies	Comparing frequencies of different alleles of one or several genetic markers between cases and healthy controls in a hypothesis-driven manner.	Inconsistent results, none specific to eating disorders, and few replications.
	Genome-wide association studies (GWAS)	Investigate the genetics of psychiatric disorders using information from and coverage of the whole genome in a hypothesis-neutral manner. GWAS focuses on common genetic variation. Can provide SNP-based heritability estimates.	Large sample sizes are necessary; first locus identified via GWAS for AN; samples needed for other eating disorders.

more robust results within psychiatry [19]. To date, only genome-wide studies in AN have been completed; thus, we focus our review on studies on AN. In AN, we recently identified the first genome-wide significant locus on chromosome 12 using association techniques in eating disorders [20].

Given the recent GWAS findings in eating disorders, we discuss basic concepts related to the genetic architecture of complex psychiatric disorders and the interpretation of GWAS results. We then review recent findings of common and rare genetic variation from genome-wide studies in eating disorders, including studies of whole-genome association, analysis of copy number variants (CNVs), and exome sequencing to identify rare transmitted and *de novo* variation. We also discuss infrastructure necessary for genetic advancement of precision medicine for eating disorders. Last, in order to transition from bench to bedside, we consider 1) the promise of these genetic findings; 2) effective ways to discuss novel findings with patients and families, and use of genetic counselors; and 3) reconceptualization of the disorders that may lead to novel ideas for treatment.

3. GENETIC ARCHITECTURE OF EATING DISORDERS

As with most psychiatric disorders, eating disorders have a complex etiology involving genetic, environmental, and population-level liability. Evidence suggests that a large number—probably hundreds to thousands—of genes contribute to the disorder, yet each gene is only responsible for a slight increase in risk [12,21,22]. Thus, eating disorders do not appear to follow the traditional Mendelian pattern of inheritance, but rather their genetic contribution is polygenic. This complex genetic architecture and poor understanding of their neurobiology has stymied linkage and candidate gene studies of eating disorders. The effect sizes of the possible genes involved in eating disorders are too small to be detected using linkage or candidate gene study designs [13,18,23,24],

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whereas their utility in the study of diseases with single gene Mendelian patterns of inheritance, such as Huntington's disease is high. Linkage studies rely on rare genetic variation (genetic risk variants that have a large effect). To detect common genetic variation, we have turned to genome-wide studies. Advances in the genetic epidemiology of eating disorders have recently been reviewed (see [12]) and are outside the scope of this review.

4. INTERPRETING GENETIC VARIATION FROM GENOME-WIDE STUDIES

As humans, we share a large section of our genome and hence a substantial amount of genetic variation [25]. GWAS are designed to identify these common genetic variants (present in more than 1% of the genome) that individually confer a small increased risk of illness but that added together may account for a substantial fraction of the heritability of a particular condition. Since 2005, GWAS has become a staple in human genetics research, with 2940 published studies curated in the National Human Genome Research Institute (NHGRI)–European Bioinformatics Institute (EBI) catalog of published GWAS (the GWAS Catalog) [26–28] as of May 2017. Likewise, over 36,066 SNPs have been identified that are associated with one or more trait(s).

Identification of risk variants and loci via GWAS indicates that a genetic region is associated with disease status. However, the identification of risk loci via GWAS does not necessarily mean that the actual susceptibility of genes at these loci have been confidently identified. Genotypes at neighboring DNA variants often correlate within a population, known as linkage disequilibrium (described in detail in section 6.1), and association signals can span large genomic regions with more than one gene. Identifying the underlying causal variants and their biological effect is a considerable challenge.

5. COMMON GENETIC VARIATION FROM GENOME-WIDE STUDIES IN EATING DISORDERS

Microarray technology has provided a powerful tool for studying the genetic contribution of eating disorders and allows for the measurement of gene expression levels genome-wide. We review a number of recent studies using genome-wide association approaches to identify genes or pathways of genes in AN.

5.1. Whole-Genome Association Studies

The first GWAS for AN was conducted by the Children's Hospital of Philadelphia (CHOP) and the Price Foundation Collaborative Group [29]. Given the small sample size (1,033 AN cases; 3,733 pediatric controls) and genetic architecture of psychiatric disorders (see above), no SNPs reached genome-wide significance ($p \leq 5x10^{-8}$). Also complicating the design was the fact that the control group had not yet passed through the age of risk for developing AN (M = 12.75 years; SD = 4.2 years) and so were effectively unscreened for eating disorders and other genetically related psychiatric problems, resulting in decreased statistical power to detect association.

The second AN GWAS was performed by the Genetic Consortium for Anorexia Nervosa (GCAN) as part of the Wellcome Trust Case-Control Consortium 3 (WTCCC3). This GWAS included 2,907 AN cases of European ancestry and 14,860 ancestry-matched female controls. Although this was a larger study, it is still a modest sample size for GWAS and no genome-wide significant loci were detected, although when 72 independent markers with the lowest p values were selected for replication, sign tests revealed that a highly significant 76% of these markers yielded results in the same direction in the discovery and the replication sample [30]. These tests encouraged the field to continue GWAS efforts as it suggested that the significant signal did exist in the data, but larger samples were required for detection. The controls selected for this GWAS were also not ideal. Although they were selected to be ancestrally compatible, they had been genotyped on similar (but not identical) platforms and at different times and in different laboratories.

In an effort to unite research groups and consolidate findings, the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) was established in 2013. The first analysis of the combined CHOP and WTCCC3 datasets emerged in 2016, and has reported the first genome-wide significant locus for AN in an area that harbors genes previously implicated in type 1 diabetes and other autoimmune disorders on chromosome 12 [20]. The GWAS comprised 3,495 cases and 10,982 controls and now has been imputed to Phase 3 of 1000 Genomes Project to enable association statistics at millions of un-genotyped variants to be calculated [25].

There is no question that GWAS has rapidly accelerated scientific advancement in the field of psychiatric genetics [31], yet, limitations of the method should also be acknowledged. First, psychiatric diagnoses made from formal diagnostic criteria, such as the DSM-5 [6] or the International Classification of Diseases (ICD-10) [32], are based on symptom clusters derived from clinical and empirical observations. Psychiatric nosology does not necessarily reflect genetics, biology, or neuroscience. Biomarkers of illness in psychiatry are lacking. Approaches such as the Research Domain Criteria (RDoc) attempt to overcome this issue via a biologically-informed remodelling of psychiatric nosology [33]. GWAS can address this problem by investigating clinical subtypes of psychiatric disorders (e.g., restricting or binge-purge AN), symptom-based analyses (e.g., symptom scores derived from questionnaires), or presumed endophenotypes (e.g., brain structures). Unfortunately, much larger sample sizes are required with these approaches.

Second, significant hits, or 'loci', identified through GWAS mark regions of the genome, but do not directly identify the genes themselves nor their causal alleles. The associated loci often are non-coding or harbour several genes, complicating the identification of a causal variant contributing to disorder risk. Furthermore, the effect sizes of the association between these loci and the disorder are small and mostly do not exceed odds ratios of 1.2. Given that these are complex traits, influenced by hundreds and possibly thousands of genes, small effect sizes are to be expected [34]. However, genetic variation acting in an additive manner is only one piece of the total genetic puzzle. Many genetic

mechanisms act in concert, such as common and rare genetic variation, gene-environment interactions mediated by epigenetic factors including DNA methylation, histone modification and non-coding RNAs, and hormonal factors, which directly bind DNA motifs and may change gene expression. Ultimately, the contribution of all of these factors needs to be investigated by a systems biology approach [35]. GWAS, thus, does not represent an end-point, but rather a stepping-stone for subsequent complex analyses and novel pathway discovery.

6. NEW TECHNIQUES FOR CAPTURING POLYGENICITY OF EATING DISORDERS

Polygenicity is the aggregate effect of genetic variants (possibly thousands) within a disease. Polygenicity is often too small to be picked up in GWAS, but contributes to disease liability [36]. It is believed that environmental factors (i.e., internalization of the societal thin ideal in eating disorders) contributes, but it is unknown how this plays out in each individual. New techniques to capture polygenicity are rapidly being developed.

6.1. Linkage disequilibrium score regression

A pattern of linkage disequilibrium (LD) across the whole genome is exploited to derive heritabilities and genetic correlations. If two genes are in linkage disequilibrium, it means that certain genomic regions are inherited together more often than would be expected by chance (e.g., genes that located close to each other on the same chromosome). The genetic overlap between two disorders or traits is referred to as the genetic correlation. SNPs contribute in two ways to a phenotype. The SNP on its own has a partial contribution to the phenotype, but also all variants which are in LD with that index SNP contribute to the phenotype. SNPs in chromosomal loci of high LD therefore are more likely to be in LD with a variant that may have a true effect on the phenotype. SNPs in this chromosomal loci of high LD may on average contribute more to the phenotype. A variety of methods to analyze genome-wide studies have been developed from LD-score regression. Genome-wide studies using LD-score regression methods in eating disorders are reviewed below.

6.2. Genome-wide SNP-based heritability and partitioned heritability

Heritability refers to the proportion of phenotypic variance in a population attributable to additive genetic factors [37]. Twin based heritabilities in eating disorders are estimated between 40% to 65%. GWAS results can also be used to calculate so-called SNP-based heritabilities which describe the total phenotypic variance explained by common genetic variants using LD-score regression [38]. The SNP-based heritability for AN derived from the most recent GWAS is estimated to be 20% meaning that 20% of the liability to develop AN is attributable to common genetic variants. Furthermore, it is possible to divide this heritability by cell-type groups, yielding partitioned heritability [39]. Partitioned heritability analysis tests the contribution of each cell-type group to the SNP-based heritability. The sample size of the current GWAS on AN was too small and therefore underpowered to estimate significant partitioned heritabilities.

6.3. Genetic correlations

Two traits or disorders can share genetic variants which contribute to their genetic liability. If a genetic variant contributes to more than one trait this variant is assumed to be pleiotropic. The degree of shared genetic contribution is approximated by genetic correlations. Genetic correlations can be estimated by an analytical extension of LD-score regression. AN shows a broad range of genetic correlations which can be split into major sub-categories: personality, psychiatry, education, anthropometry, glucose, and lipid metabolism. AN exhibited positive genetic correlations with neuroticism, schizophrenia, educational attainment, and lipid measures [20]. These correlations suggest shared genetics between those traits.

The positive genetic correlation with neuroticism—a personality trait associated with anxiety and major depression—may partly explain the comorbidity between AN and mood disorders. A positive genetic correlation reflects the same genes influencing both target traits in the same direction. Thus, a genetic variant that increases one's liability to score high on a neuroticism scale also may increase one's chance of developing AN. Genetic correlations are dependent on the SNP-based heritability of both traits. Higher SNP-based heritabilities decrease the corresponding standard error of a genetic correlation, indicating the precision of a heritability estimate. Conversely, a higher standard error indicates a lower precision of the heritability estimate. Varying measures of neuroticism yield SNP-based heritabilities between 3%-8% [40,41] resulting in genetic correlations of 0.39 (SE=14) and 0.28 (SE=0.06) with AN [20].

Whereas, the genetic overlap with schizophrenia may implicate a psychotic component to the disorder which may express itself in the disturbed body image observed in clinical samples. The positive genetic correlation with years of education and attending college may reflect the increased perfectionism which is observed in AN.

Surprisingly, high-density lipoproteins showed a positive genetic correlation with AN. They are widely recognized as a positive marker of cardiovascular health. Measures of an unfavorable glucose metabolism such as insulin resistance, β-cell function, and fasting insulin, as well as glucose were negatively genetically correlated with AN suggesting that AN may represent a status of increased insulin sensitivity with reduced insulin production. Furthermore, negative genetic correlations with measures of body adiposity were observed, suggesting that the same genetic variants may influence extremes of body adiposity in both directions [20]. This pattern of genetic correlations encourages a reconceptualization AN as an illness that contains both psychiatric and metabolic components. Post-GWAS investigations are needed to explore mechanisms of metabolic action that may contribute to the perplexing catastrophic and often precipitous weight loss in susceptible individuals. To extend the findings of GWAS, the exploration of disorder-associated genomic regions is important by, for instance, fine mapping or exome sequencing to identify causal variants in genes. Moreover, investigations, such as large-scale proteomics and lipidomics could be applied to deeply

phenotype patients suffering from any kind of eating disorder. These methods can identify altered levels of metabolites on a systems biology level and help us to understand the severe weight and appetite dysregulation observed in eating disorders, especially in AN.

6.4. Polygenic risk scores.

Single SNP analysis do not fully capture the polygenic architecture of psychiatric disorders. Polygenic risk scores (PRS), however, can be used to incorporate several SNPs, which are associated most strongly with an eating disorder, into an overall composite score. Software like PLINK, PRSice, or GCTA can be used for these computations [42–44]. These composite scores have three main applications: within-trait association, cross-trait association, and prediction. First, we can determine if genome-wide identified polygenic risk scores are associated with the same trait in a second cohort (i.e., within-trait association, external validation of the phenotype). The typical procedure to derive polygenic risk scores consists of a discovery sample and a target sample. The polygenic risk score is calculated in the discovery sample and then used to predict cases in the target sample. Second, polygenic risk scores can be applied to assess the genetic overlap between disorders and traits (cross-trait association). A polygenic risk score can be used to replicate genetic correlations between traits (i.e., educational attainment) and phenotypes (i.e., AN) which were calculated by LD-score regression. In the case of educational attainment and AN, a higher polygenic risk score for educational attainment should also predict case status in AN. Last, if a temporal aspect is added to the prediction models in which polygenic risk scores are used, it may be possible in the future to predict disease onset, course of the disorder, optimal treatment, and possibly treatment response [45].

After investigating the polygenic architecture of eating disorders, two questions remain: First, why do all related individuals with a similar genetic background develop eating disorders? Second, what contributes to individual differences in susceptibility to environmental stressors and protective factors? Polygenic risk scores can facilitate our understanding of gene-environment interplay and address these open questions. Progress in this area is limited by the scarcity of genotyped and longitudinally phenotyped study populations with sufficient numbers of participants [46].

To date, only one study applying polygenic risk scores within anorexia nervosa has been completed. The AN polygenic risk score was derived from the most recent AN GWAS and was used to predict the ability to recognize facial emotions, which has been shown to be disrupted in psychiatric disorders broadly [47,48] and AN specifically [49,50]. In the study the polygenic risk score for AN did not predict the ability to recognize facial emotions in others [51]. However, the study had several limitations. First, in this sample, facial emotion recognition did not yield an estimate for heritability. Second, the study population may be too young for the phenotype studied as the average age was 8.5 (SD = 1.0) and largely pre-pubescent. This is key as facial emotion recognition increases after puberty [52]. Third, the phenotype measure exhibited modest internal consistency for the identification of all faces and even lower internal consistency for specific emotions. Finally, the original AN GWAS had a low sample size decreasing power of the polygenic risk score as such. Further studies using polygenic risk scoring are needed to investigate the polygenic architecture of eating disorders and its predictive value.

6.5. Gene-wise analysis and pathway analysis.

Systems biology approaches can be applied to the results of GWAS to understand the underlying biology of eating disorders. It is important to link identified risk loci to biological pathways. This linking can help find relevant biological processes, cell types and brain circuits involved in eating disorders. Two types of analyses are normally conducted: gene-wide analysis and pathway analysis using software like MAGMA, INRICH, and ALIGATOR [53]. GWAS summary statistics are exploited to identify genes or whole pathways that are more strongly associated with the phenotype compared with all other genes or pathways in a set. To date, there are different sets of biological pathways depending on which databases are used to generate those pathway sets, such as Reactome, GO database, KEGG pathway database, and MSigDB [54,55]. Larger sample sizes are needed to identify significant genes or pathways associated with AN.

7. RARE GENETIC VARIATION IN GENOME-WIDE STUDIES OF EATING DISORDERS

In contrast to common genetic variation, rare genetic variation is assumed to have larger biological impact on the phenotype. Rare genetic variation is defined to occur at a frequency lower than 1% in the population. This includes very rare or private variants with a frequency below 0.01%, and copy number variants (CNVs), which can be inherited or *de novo* (non-inherited).

7.1. Copy number variation

Two genome-wide analyses of CNVs have been conducted in AN. There are no other analyses of CNVs covering the other eating disorders. In the first, no evidence emerged supporting enrichment of AN cases for CNVs above controls, and rare or large CNVs were not notably overrepresented in AN cases [29]. A novel and recurrent 13q12 deletion (1.5 Mb) disrupting *sacsin molecular chaperone* (*SACS*) was seen twice in cases and CNVs disrupting the *contactin 6/contactin 4* (*CNTN6*/*CNTN4*) region were found in multiple cases, although the study lacked significant sample size to detect rare pathogenic CNVs. In the second, a case-only genome-wide CNV survey explored whether pathogenic CNVs implicated in other psychiatric and neurodevelopmental disorders were also observed in AN cases [56]. Four of these well-established pathogenic CNVs (deletions or duplications in 1q21.1, 7q36.3, 15q13.3, or 16p11.2) were found in a small number of AN cases. One case also had a large deletion in the 13q12 region [56], and 41 cases had deletions or duplications which were 1 Mb or larger. However, at this point it is not clear whether large effect CNVs play a demonstrable role in AN. Larger sample sizes are required to detect the effect of rare CNVs.

8. TOWARDS PRECISION PSYCHIATRY IN EATING DISORDERS

GWAS represent a starting point for genetic discovery which may lead to precision psychiatry. In some ways, eating disorder treatment has consistently utilized precision medicine approaches; providers integrate signs and symptoms, scientific evidence, their own training and expertise, and patient needs in order to facilitate a treatment plan. New models of precision medicine emphasize the use of an individual's genetic information and measurable biomarkers to optimize treatment [57]. The significance of these discoveries lies in their potential ability to identify a causal link from gene to cellular and molecular mechanisms underlying eating disorder symptoms.

The coming year marks thirty years of evidence for the genetic basis of eating disorders [58] and as a field, we are just at the beginning. Identification of the genetic mechanisms underlying AN from genome-wide studies has just begun, yet are obsolete all other eating disorder subtypes. The future of eating disorder identification and treatment will depend on the timely transition of research findings into more effective and efficient care. The identification of the underlying polygenic architecture of AN, for instance, could enable healthcare providers to estimate a genetic liability to develop AN later in life. A polygenic liability, however, does not equal a deterministic factor. Individuals with a high genetic liability can be buffered by an advantageous and beneficial environment and possibly never express their genotypic risk, but the opposite is also possible. Individuals with a low genetic liability may be exposed to disadvantageous and precipitating environments, and be exposed to several stressors which trigger the development of an eating disorder to which they are only minimally genetically susceptible. As new findings from the genetics of eating disorders emerge, these message of disease liability (rather than disease determination) should be translated to patients and families. As genetic information about eating disorders reaches the general population, patients and families understandably raise questions about transmission of eating disorders to the next generation. It is often assumed that genetic counselors only play a role in transmission of Mendelian inherited diseases; however, this is untrue. Genetic counselors play a meaningful role in counseling individuals about transmission of disorders with complex inheritance patterns such as psychiatric illnesses [59]. As such, it is of value to engage genetic counselors sooner as these questions are arising clinically with increasing frequency.

Apart from risk prediction, genomic tools to capture the polygenic architecture of eating disorders may allow for characterization of new subtypes and resulting tailored treatments. For example, genetic risk profiles may differentiate between psychiatric, metabolic, or activity-based subtypes of AN. These subtypes may be distinguishable by their different genetic profiles. Applying the most efficacious treatments, or new treatments developed specifically to emerging biologically-based subtypes, may maximize our ability to target treatments to causes. Additionally, the presence of genetic differences or similarities may also explain the high diagnostic crossover between eating disorder presentations. For example, early detection of risk that presages transition from AN to BN, could flag the importance of clinicians working toward resolution of AN symptoms without precipitating migration to BN. Although this should always be the clinical goal, at present our ability to predict who will experience diagnostic crossover is limited [60–65].

To reach these aims and best serve our patients, facilitation of international collaboration in the eating disorders field is a must. We need to conduct GWAS covering all other eating disorders, especially BN and BED. GWAS of all eating disorders could enable the health care providers to identify not only eating disorder trajectories such as diagnostic crossover, but also risk for chronicity, adverse somatic outcomes, and risk of death. Treatment of eating disorders is challenging for providers, for families, and for patients as evidence-based treatments are limited and optimal treatment prediction models sparse. GWAS datasets encompassing all eating disorder phenotypes may assist in choosing the optimal treatment to facilitate full recovery and avoid crossover and adverse outcomes.

8. CONCLUSION

We are at the very beginning of conceptualizing precision medicine initiatives with genomic information. Genomic discovery in AN is accelerating rapidly, but work on BN and BED is woefully behind. Very large sample sizes (in the tens of thousands) are key to discovering genetic variants associated with risk, and global cooperation is underway to achieve such sample sizes. Advances in genomic methods, coupled with increasing knowledge about environmental risk factors, will provide a more complete and accurate picture of eating disorder etiology and allow us to move rapidly toward personalized treatment.

CONFLICT OF INTEREST

CM Bulik reports: Shire (grant recipient, Scientific Advisory Board member) and Pearson and Walker (author, royalty recipient).

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