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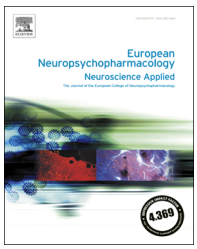

Contemporary views on the genetics of anorexia nervosa

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Abstract
Anorexia nervosa (AN) is a serious mental illness characterized by severe dietary restriction that leads to high rates of morbidity, chronicity, and mortality. Unfortunately, effective treatment is lacking and few options are available. High rates of familial aggregation and significant heritability suggested that the complex etiology of AN is affected by both genetic and environmental factors. In this paper, we review studies that reported common and rare genetic variation that influence susceptibility of AN through candidate gene studies, genome-wide association studies, and sequencing-based studies. We also discuss gene expression, methylation, imaging genetics, and pharmacogenetics to demonstrate that these studies have collectively advanced our knowledge of how genetic variation contributes to AN susceptibility and clinical course. Lastly, we highlight the importance of gene by environment interactions (G × E) and share our enthusiasm for the use of nutritional genomic approaches to elucidate the interaction among nutrients, metabolic intermediates, and genetic variation in AN. A deeper understanding of how nutrition alters genome stability, how genetic variation influences uptake and metabolism of nutrients, and how response to food components affects disordered eating, will lead to personalized dietary interventions and effective nutraceutical and pharmacological treatments for AN.

1. Introduction

Anorexia nervosa (AN) is one of the three formally recognized eating disorders by the American Psychiatric Association in the fifth edition of the Diagnostic and Statistical Manual. AN is a disorder that predominantly affects females (Micali et al., 2013), and is characterized by severe dietary restriction and emaciation that lead to high rates of morbidity, chronicity, and mortality (Arcelus et al., 2011; Chesney et al., 2014; Strober et al., 1997). The pathophysiology and etiology of this disease are unclear, although psychosocial factors have been traditionally speculated as important contributory factors to AN (Lucas, 1981; Woodside, 1993, 1995). Twin and family

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studies found high heritability estimates, demonstrating significant contribution of genetic factors in AN. The familial aggregation (Steinhausen et al., 2015; Strober et al., 2000) coupling to evidence of heritability (Bulik et al., 2006; Thornton et al., 2011; Wade et al., 2000) further strengthens the "biopsychosocial entity" disease model (Lucas, 1981) of this serious illness.

Although AN is less common (prevalence of 0.5–3%) than bulimia nervosa (1–3%) and binge eating disorder (2.4%) (Hoek, 2006; Smink et al., 2012), it is the deadliest eating disorder with an all-cause mortality ranked higher than all other psychiatric disorders with the exception of substance abuse and postpartum depression admission (Chesney et al., 2014). The search for genes that predispose individuals to AN began more than 18 years ago (Campbell et al., 1998; Collier et al., 1997; Hinney et al., 1997a) during an upsurge of interest in discovering what role 5-hydroxytryptamine (5-HT) neurotransmission system plays in the genetics of psychiatric disorders. However, despite years of intensive research and multiple promising leads, not a single gene has been proven as a major risk factor. Furthermore, none of the associated markers found in individual studies has led the way into changing clinical practice.

The primary objective of this review is not to provide an extensive account of the numerous studies done to date. Rather, we aim to illustrate the etiologic uniqueness of AN by highlighting a subset of genetic and related studies and discussing future directions that can translate information on genetic underpinnings into clinical practice. We present these data threaded through a narrative of key genetic and genomic concepts including basic concepts of human genetics and genomics, twin and heritability studies, linkage and association study designs, candidate genes and genome-wide association studies, gene expression and epigenetics such as DNA methylation, gene by environment ($G \times E$) interactions, and the use of multi-domain omics markers to understand molecular functions of genetic risk factors. These genomic- and genetic- factors function together, playing an instrumental role in shaping AN susceptibility, illness course, and outcome. We further propose the use of nutritional genomic approaches (Mutch et al., 2005) to understand how nutrition alters genome stability, how genetic variation influences uptake and metabolism of nutrients, and how response to food components affects disordered eating. Successful implementation of gene-nutrient interaction studies will assist in developing necessary insights into causes and mechanisms of AN, leading to improved etiological understanding of AN, and result in better intervention and treatment strategies.

2. Human genetic variation

The advancement of the Human Genome Project has allowed researchers the use the genome's natural variation to study human biology (Lander et al., 2001). A typical protein-coding gene consists of coding exons that are translated into protein, untranslated regions (UTRs) in the upstream (5-UTR) and downstream (3-UTR) of the transcript region that often contain regulatory control elements that may influence transcriptional efficiency, and several intron regions that may affect alternative splicing of the mRNA. The most common type of genetic variation is termed single nucleotide polymorphisms (SNPs). The first reports linking 5-HT system to AN (Collier et al., 1997; Hinney et al., 1997a) examined common SNPs in the promoter region of the 5-HT2A receptor gene and the 5HT-transporter-linked polymorphic region (5-HTTLPR).

Other sequence variations of interest include microsatellites, which are short or long repetitions of the same sequence motif in tandem (Ellegren, 2004), and insertions or deletions as well as structural variants that affect large chromosomal regions (MacDonald et al., 2014). The microsatellite markers that were found to associate with AN and related phenotypes include allele 13 of the marker D11S911 in the UCP-2/UCP-3 locus in Caucasian women (Campbell et al., 1999), but the association could not be replicated in a sample of Japanese AN patients (Ando et al., 2004). A promoter region microsatellite of AVPR1A, RS3, was associated with Dieting subscale of the Eating Attitudes Test (EAT), and Drive for Thinness subscale of the eating disorders inventory (EDI) (Bachner-Melman et al., 2004). Other studies focused on body weight (Yilmaz et al., 2014) and specific cognitive and behavioral dimensions such as drive for thinness, body dissatisfaction, personal ineffectiveness, perfectionism, and harm avoidance as "subphenotypes" of AN (Frieling et al., 2009; Frieling et al., 2006; Gamero-Villarroel et al., 2015; Mikolajczyk et al., 2010; Root et al., 2011). Identification of AN subphenotype-associated genetic markers may facilitate the discovery of novel susceptibility genes and biological pathways.

The majority of the sequence variation in the genome are located in the introns and are traditionally thought of as "nonfunctional" variants and "neutral" markers. However, intronic variants may affect alternative splicing of the mRNA or act as enhancer of the gene to affect expression of other genes (Pagani and Baralle, 2004). Examples of intronic variants that were implicated in AN risk were identified in the largest meta-analysis of genome-wide association study (GWAS) for AN to date, which comprised of 5551 cases and 21,080 controls (Boraska et al., 2014). Although not meeting the strictest threshold of genome-wide significance ($10(-8)$), SOX2OT intronic variant rs9839776 ($P=3.01 \times 10(-7)$) and PPP3CA intronic variant rs17030795 ($P=5.84 \times 10(-6)$) were the most significantly associated variants in this study (Boraska et al., 2014). It is important to note the phenomenon of linkage disequilibrium (LD), which refers to high correlation among segments of physically close polymorphic sites in the genome. The implication of LD is that the "causal variant" associated with a disease may be "captured" by the detection of a "proxy marker" that is in high LD with the causal variant. Therefore, the two intronic variants reported may be proxy markers for other unscreened yet biological relevant functional variants.

Sequence variation within regulatory regions of the gene, such as promoter and 3'-UTR regions, may form motifs that can affect the gene product by modulation of transcriptional efficiency or post-transcriptional stability. Allelic variants that disrupt these motifs may therefore alter gene expression or protein levels to affect phenotype. In our candidate gene exon-sequencing study (Scott-Van Zeeland et al., 2014), the over-representation of rare variants revealed the EPHX2 as an AN susceptibility gene. Moreover,

AN-associated EPHX2 3'-UTR SNP (rs1042064) contains micro RNA (miRNA) sequence motif for hsa-miR-512-3p. A potential functional role of this 3`-UTR SNP is suggested by the results from the bioinformatics analysis (Brodskii et al., 1995), which predicted that the free energy of mRNA was −44.5 kkal/mol for the protective C allele and −38.5 kkal/mol for the T allele. The difference suggests a more stable mRNA structure for the C allele, which could affect binding of regulatory elements such as hsa-miR-512-3p (Yue et al., 2009).

3. Family-based study design: twin and linkage studies

Evolution of the genetic investigation for AN has expanded greatly since the observations of increased twin concordances (Askevold and Heiberg, 1979; Klump et al., 2001b; Lilley and Silberg, 2013) and heightened risk of developing AN in first degree relatives of those affected (Strober et al., 2000). Numerous linkage and association studies followed with the goal to identify genes that contribute to AN risk. While twin and family studies provide a clear evidence of genetic contribution to AN risk, heritability estimates have varied (Ben-Dor et al., 2002; Bulik et al., 2006; Thornton et al., 2011). This is likely due to limitations such as insufficient follow-up period of twin pairs (e.g., initial discordant pairs turn to be concordant pairs at a later time) (Boomsma et al., 2002), inconsistent diagnostic criteria, sample heterogeneity, and biased methodological assumptions (Benchek and Morris, 2013).

Linkage studies use families with multiple affected individuals to examine large segments of genetic markers across the genome to assess if any are "linked" to AN (Grice et al., 2002; Kaye et al., 2000). Using a more homogeneous sample of restricting-AN subtype, chromosome 1p surfaced as the most promising region for AN (Grice et al., 2002). Using covariates of obsessionality and drive for thinness, linkage was replicated for chromosome 1, and found also in chromosomes 2, 10, and 11 (Devlin et al., 2002). An explosion of candidate association studies then followed in search of individual genes thought to be responsible for AN, both within the linkage regions previously reported, and in suspected biological pathways that are thought to affect disordered eating.

4. Candidate genes and genome-wide association studies (GWAS)

AN is unlikely to follow a Mendelian inheritance, therefore, the most commonly used strategy to identify genes of predisposition has been genetic association analysis. The candidate gene association studies have been eloquently and comprehensively reviewed by many others (Ben-Dor et al., 2002; Brandys et al., 2015; Clarke et al., 2012; Helder and Collier, 2011; Hinney et al., 2000; Klump et al., 2001a; Monteleone and Maj, 2008; Rask-Andersen et al., 2010; Slof-Op't Landt et al., 2005) therefore we will not be repeating these reviews. Instead, we will summarize a subset of studies, and offer our conjecture as to why successful identification of risk genes has been difficult.

Candidate gene association studies encompass sets of genes that are either hypothesized to be relevant to the biological systems involved in AN pathophysiology, or are mapped on chromosome regions previously identified through linkage studies. The biological systems most often examined include the dopaminergic system (Bachner-Melman et al., 2007; Bergen et al., 2005; Bruins-Slot et al., 1998; Hinney et al., 1999b; Kontis and Theochari, 2012), the serotonergic system (Ando et al., 2001; Calati et al., 2011; Campbell et al., 1997, 1998; Castellini et al., 2012; Chen et al., 2015; Collier et al., 1997; Ehrlich et al., 2010a; Fumeron et al., 2001; Gervasini et al., 2012; Hammer et al., 2009; Han et al., 1999; Hinney et al., 1997a; Hinney et al., 1999a; Karwautz et al., 2011; Kiezebrink et al., 2010; Levitan et al., 2001; Martaskova et al., 2009; Nishiguchi et al., 2001; Rybakowski et al., 2006; Slof-Op't Landt et al., 2013; Sundaramurthy et al., 2000), the noradrenergic system (Frieling et al., 2006; Frisch et al., 2001; Hinney et al., 1997b; Mikolajczyk et al., 2010, 2006), the appetite control system (Dardennes et al., 2007; Gamero-Villarroel et al., 2015; Quinton et al., 2004; Rask-Andersen et al., 2010; Rosenkranz et al., 1998b; Shih et al., 2015; Simler et al., 2006), and hormones (Cui et al., 2013; Eastwood et al., 2002; Kim et al., 2014; Rosenkranz et al., 1998a; Slof-Op't Landt et al., 2014; Versini et al., 2010; Zhang et al., 2013) among others (Ando et al., 2014; Clarke et al., 2014; Cui et al., 2013; Czerniak et al., 2013; Scott-Van Zeeland et al., 2014; Yilmaz et al., 2014).

While several associations between candidate gene polymorphisms and AN have been reported with modest effect sizes, relatively few of these associations have been replicated, and none has been replicated consistently. Similarly, the published AN genome-wide association studies (GWAS) have yet to show significant findings for AN (Boraska et al., 2014; Wang et al., 2011). The reason for a lack of success in replicating and identifying associations found in candidate gene studies and GWAS is complex. A lack of sufficient sample size likely explains the disappointment of the AN GWAS efforts to date, as typically thousands of subjects are needed to yield significant loci. For example, schizophrenia GWAS efforts have only recently led to identification of 108 risk loci and novel biological pathways with a study sample composed of 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The PGC-AN group has recently presented the result from their largest GWAS of European ancestry to date at the 2015 World Congress of Psychiatric Genetics. Using 4118 cases and 17,584 controls, three distinct loci were found to exceed genome-wide significance for AN association (Anorexia Nervosa Working Group of the PGC et al., 2015). Together, these findings suggest that the same level of success found in schizophrenia GWAS could also be achieved for AN given adequate sample sizes.

In addition to the sample size and clinical heterogeneous issues, the complexity of gene interaction and regulatory effects to other genomic factors have not been successfully accounted for. For example, the genes in the serotonergic and noradrenergic systems have been examined as independent risk genes to AN. However, perturbation of these systems is likely a result of complex interaction and compensatory mechanism with other neurobiologic systems and brain regions. Clarification of each individual risk gene's role within these systems is understandably difficult without

first accounting for the system-wide perturbation. Likewise, identification of AN-associated genetic/genomic markers without sufficient knowledge of how the markers affect brain circuitry and behaviors is unlikely to yield a greater understanding of symptomatology. For these reasons, the research field has begun to examine the contribution of candidate genes through their "dynamic presentation" such as gene expression and methylation.

5. Alteration of gene expression: mRNA and methylation

Gene expression is the process by which genetic instructions are used to synthesize gene products. Changes in the mRNA expression have been reported in atrial natriuretic peptide (ANP) (Frieling et al., 2008), cannabinoid 1 receptor (CB1) (Frieling et al., 2009), proopiomelanocortin (POMC) (Ehrlich et al., 2010b), and dopamine transporter (DAT) and D2 receptor (DRD2) (Frieling et al., 2010) genes in individuals with AN. Additionally, the expression of leptin receptor-coding gene was shown to differ significantly both between binge-purge AN subtype (AN-BP) and restricting subtype (AN-R) patients, and between AN-R and control subjects (Janas-Kozik et al., 2008). In assessing the change of gene expression before and after weight restoration, Kim et al. (2013) found CYP11A1, C16orf11, LINC00235, and CPA3 to be down-regulated after weight restoration while multiple olfactory receptor genes (OR52J3, OR51L1, OR51A4, and OR51A2) were up-regulated. While these expression changes may not be directly relevant to AN susceptibility and relate more to disease processes, they revealed pathway targets that may be investigated for potential new therapy.

Transcriptomic profiling has been conducted for inflammatory cytokine candidates in AN. Kahl et al. observed an increase in TNF-α and IL-6 expression in AN at hospital admission time compared with controls, and TNF-α remained significantly higher while IL-6 expression decreased in weight-restored patients (Kahl et al., 2004). In studies on expression of P-glycoprotein (Storch et al., 2008) and prohormone preproenkephalin (ppE mRNA) (Weiss et al., 2010), neither study could identify evidence to support a significant difference between AN and healthy controls, although ppE mRNA level was negatively associated with depressive and anxious symptoms (Weiss et al., 2010).

Epigenetics, such as methylation, refers to external modifications to DNA that turn genes "on" or "off". These modifications alter the physical structure of DNA without a change to the DNA sequence. Ehrlich et al. identified peripheral POMC mRNA expression decreasing with malnutrition and hypoleptinemia in AN, and found methylation of single CpG residues in the E2F binding site to be inversely related to POMC expression (Ehrlich et al., 2010b). Methylation status of the CpG sites within the exon 1 to the MT2 regions of oxytocin receptor (OXTR) gene was examined, and six methylated CpG sites were found to be significantly different between AN and controls while five CpG sites were associated with body mass index and eating disorders psychopathology (Kim et al., 2014). Epigenetic studies also suffer from power issues as candidate gene studies have in detecting reproducible associations. For example, while Tremolizzo et al. (2014) identified a modest yet significant reduction of global DNA methylation in AN, Saffrey et al. (2014) reported no alterations in global or gene-specific DNA methylation. Yet, a most recent study by Booij et al. (2015) reported a higher global DNA methylation in AN groups compared to controls.

6. Epistasis, gene by environment interactions (G × E), and the era of nutritional genomics

It is well established that genes do not function alone but exert effects on disease traits together with other genes (G × G interaction or epistasis) and through interactions with environmental factors (G × E). In AN, a study examining 151 TagSNPs covering 10 neurotrophin signaling genes discovered that NGFB was shown to modify AN risk conferred by the NTRK3 rs7180942 risk genotypes by a synergistic epistatic interaction (Mercader et al., 2008). In another study, the risk of developing AN increased up to 8-fold when certain variants within monoamine oxidase A (MAOA) and serotonin transporter (SERT) genes were preferentially transmitted together to affected offspring compared to the risk imposed by the MAOA variant alone (Urwin and Nunn, 2005). In a family-based sequencing study of two large pedigrees affected with mixed eating disorders, histone deacetylase 4 (HDAC4) and estrogen-related receptor α (ESRRA) genes were shown to segregate within each family (Cui et al., 2013). When the authors followed-up on the findings by a transcriptional analysis, HDAC4 transcript was found to repress the expression of ESRRA -targeted genes, while ESRRA and HDAC4 showed interaction both *in vitro* and *in vivo*. These promising data suggest a potentially important role of epistasis in eating disorder susceptibility (Cui et al., 2013).

The phenotypic expression of a genotype is dependent on a host of factors that include genetic background, age, gender, developmental-, physiological- and pathological-conditions, and behavioral factors such as the food and drug intake and physical activity. Therefore, both acute and long-term environmental factors interact and influence the expression of genetic risk to affect pathology of AN and should be considered as modifiable factors. In AN, an earlier G × E hypothesis (Bulik, 2005) suggested that anorexia may be perpetuated across generations due to maternal undernutrition during the gestational period and the passing of a genetic predisposition to offspring of mothers with AN. Indeed, the combined consequences of poor parental eating, transmission of susceptibility alleles, and environmental stressor are known to cause epigenetic changes which can lead to later onset of chronic diseases (Waterland and Jirtle, 2004). Mazzeo and Bulik (2009) eloquently described some key environmental factors to consider including family relationships, parental role modeling of eating disordered behavior, and problematic feeding behaviors. Such a phenomenon is described as "G–E correlation", as formal interaction relationships could not be easily modeled. Active G–E correlations may indeed influence genetic-based eating disorder etiology; however, without a clear picture of the resulting biological perturbation obtained from empirical data, few modifications can be made to improve deleterious effects of risk genes. There is clearly a need for formal research to study the relationship between

genes and environmental factors in order to take advantage of the modifiable factors (i.e., environmental factors, both risk and protective ones) to reduce the burden of non-modifiable factors (e.g., inherited genetic variants).

From a practical epidemiological study stand point, accurate measurement and accounting of most environmental factors (termed exposome) (Wild, 2005) are more difficult compared to genetic factors. G × E studies require a much larger sample size to ensure sufficient power given the combinations of factors in the presence of interactions. These practical challenges and the low population prevalence of AN have led to a lack of reports in gene × environmental factor studies in AN to date. Genetic variation are known to affect food preference and tolerances among human subpopulations, thereby influencing dietary requirements for optimal health and disease prevention (Pirastu et al., 2012; Stover, 2006). AN patients are in fact excellent subjects to study G × E because of their key symptom-food aversion. With the food as the key non-genetic disease risk and maintenance factor, we propose that the use of nutritional genomic approaches can yield improved understanding on how genes and diets interact to effect food aversion.

The science of nutritional genomics includes two branches, nutrigenetics and nutrigenomics (Fenech et al., 2011). Nutrigenetic studies examine the effect of genetic variation on dietary response, and explore the modifying effects of genes on macro and micronutrient uptake and metabolism. Identification of genetic variation that predisposes AN patients to specific food aversion can be established via longitudinal study designs that account for dietary factors. The alleles/genotypes that are shown to affect food aversion, biological perturbations, and effectiveness of metabolites can be used to personalize dietary counseling and guide implementations of treatment meals and refeeding. On the other hand, nutrigenomic studies aim to assess influence of nutrients on expression of genes at the levels of gene regulation, signal transduction, chromatin structure and protein function (Fenech et al., 2011). The general aim of nutrigenomics is to identify the effects of several nutrients, including macronutrients and micronutrients, on the genome (Mutch et al., 2005). Therefore, nutrigenomic studies generally require very large sample sizes to identify meaning G × E interactions. Prominent research groups such as the Psychiatric Genetics Consortium for Anorexia Nervosa (PGC-AN) are currently taking rapid and effective strategies to form larger international AN consortium for new GWAS initiatives, making now an ideal time to pursue nutrigenomic studies in AN. Nutrigenomics can also be used as a functional genomic tool to study AN-specific biological system to understand how nutrition affect metabolic disturbances and homeostatic control.

Our recent AN studies identified and replicated an association between AN and EPXH2 gene (Scott-Van Zeeland et al., 2014). A subsequent study (Shih et al., 2015) probed lipidomics changes including the endogenous substrates and metabolite products in order to evaluate the biological functions of EPHX2. This study found dysregulation in several food-based polyunsaturated fatty acids (PUFAs) and their downstream metabolites (oxylipins) in AN. The dysregulated markers were associated with AN risk and recovery, and the *in vivo* sEH enzyme activity (coded by EPHX2) was elevated in AN to drive this dysregulation. The relationship of PUFAs and sEH is the key piece of the puzzle as sEH uses PUFAs as parental substrates to produce downstream bioactive metabolites that are directly involved in the inflammatory cascade and influence health (Morisseau and Hammock, 2013). Interestingly, our most recent data showed that after eating a meal, an increase of proinflammatory metabolite was observed only in AN patients and not in healthy controls (Yang et al., 2015). Moreover, the proinflammatory metabolite increase was PUFA class-dependent. These findings suggest that inflammatory consequences of high sEH activity in AN may be diet-dependent. This is a proof of concept demonstrating the importance of biological interaction between a food-based factor and a genetic factor. Together, their interaction may exert a more powerful effect in disease risk and progression than each factor alone. Furthering this line of research will produce comprehensive information needed to identify modifiable targets for improved interventions and treatments.

The strategy of nutrigenetic and nutrigenomic investigations is an ideal solution to uncover the degree to which diet influences the disease state given an individual's genetic background. A shared goal of nutrigenomics and nutrigenetics is to identify gene by nutrient interactions that modulate disease susceptibility. These approaches incorporate multiple scales of data including biochemistry genomics (e.g., mRNA and metabolites) and human nutrition (e.g., lipids and minerals) to identify these novel interactions and elucidate the mechanisms driving persons' response to dietary components with regard to genetic differences (Subbiah, 2007). As demonstrated in our studies (Shih et al., 2015; Yang et al., 2015), the application of multiple "omics" markers (multi-omics) reveals not only a mechanism by which an AN risk gene (EPHX2) affects AN, it also provides data to support a potential benefit of nutritional intervention for individuals harboring high sEH-expressing variants. Therefore, consequences of AN genetic vulnerability may be managed by appropriate environmental alterations (e.g., dietary modification or supplementation). As such, nutraceuticals may also be developed for genetically at-risk individuals in AN prevention and management.

The cellular and physiological perturbations discovered through nutrigenomic and neutrogenetic studies should be validated by the use of genetically diverse animal models to clarify the biological and neuronal systems that are affected by dietary factors. With that knowledge, dietary modification recommendation or nutraceuticals can be personalized based on empirical data verified both in animal models and human randomized trials. The rapid advancement in the multi-omics technology is enabling a new chapter of genetic and genomic studies in dietary-regulation of human health. The gene-diet interaction surfaces again as a key element in the interplay between an individual's genetic background and his/her lifestyle. The advancement in biotechnology enables the generation of unprecedented "big data". With this advantage, what better and more relevant disease than AN will benefit from large-scale nutrigenomics and neutrogenetic investigations?

7. Imaging genetic and pharmacologenetic studies

Imaging genetic studies (Medland et al., 2014) map genes that effect the brain, and enhance our understanding of the

biological underpinnings of brain phenotypes altered in AN (Bailer and Kaye, 2011; Frank, 2015). With sufficient sample sizes, the imaging-genetics approach may improve how we classify eating disorders and prognosticate disorder risk and trajectory. Furthermore, coupling imaging and genetic research approaches may gain critical knowledge that improves the efficacy and safety for neuromodulation treatments for AN such as repetitive transcranial magnetic stimulation (Bartholdy et al., 2015) and deep brain stimulation (Lipsman and Lozano, 2014). Due to a lack of consensus on effective pharmacological treatment strategy (Treasure et al., 2015; Watson and Bulik, 2013), pharmacogenetic studies have yet to yield significant insights in changing treatments in the clinical setting (Adan and Vink, 2001; Gorwood, 2004; Monteleone and Maj, 2008).

8. Conclusion and future direction

The main objective of human genetic/genomic research is to gain fundamental understanding of disease pathophysiology in order to improve medical diagnosis, risk assessment, and treatment. While genome-wide analysis and candidate gene studies have not definitively confirmed any significant AN genes by consistent replications, these studies have moved our collective knowledge forward. Although we have discussed only a subset of published studies as examples in this review, we hope we have conveyed that the knowledge gained from genetic/genomic and related studies have the potential to discover new therapeutic targets that may attenuate genetic risk and modulate AN outcome. Furthermore, gene-based knowledge and the associated proteomic, lipidomic, metabolomic, or epigenomic markers may be developed into biomarkers to improve diagnostic and prognostic assessments. The collective knowledge may considerably modify the treatment and relapse-prevention approach of AN as new translational and cross-disciplinary research approaches emerge.

As it remains undeniable that food continues to be the superior treatment for AN (Woodside, 1995), knowledge of the genetic basis of physical processing and psychological acceptance of food is valuable not only to improve feeding-based treatments and weight restoration (Marzola et al., 2013), but also to develop more effective personalized nutraceutical and pharmaceutical interventions. A focused effort to understand gene-diet interactions in AN will lead to a more personalized treatment approach and promote discovery of novel nutritional and pharmacological interventions.

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Contributors

Authors PBS and DBW designed the paper. PBS managed the literature searches and wrote the first draft of the manuscript. DBW provided subsequent input and review. All authors contributed to and approved the final manuscript.

Conflict of interest disclosures

None.

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