GENETICS IN ANOREXIA NERVOSA

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Abstract

Anorexia Nervosa (AN) in defined by restriction of energy intake leading to low body weight, an intense fear of gaining weight, as well as body image disturbance. AN has the highest mortality rate of any psychiatric disorder and unfortunately, treatment methods are often inefficient. Genetic factors have a substantial role in the etiology of AN. The purpose of this review is to make a brief synthesis of the current knowledge regarding the genetic factors involved in AN disorder. Several studies that have an impact in understanding the role of genetics in the AN architecture were discussed and chronologically presented. As AN represents a difficult treat-to treat illness, all the research that has been made until now was led by the motivation and goal of finding specific pharmaceutical targets for the treatment and prevention of AN. Although there has been made substantial progress in understanding the genetic architecture of AN and its relation to other disorders, further investigation still needs to be done with hope and determination.

Keywords: Anorexia Nervosa, GWAS, SNPs, genes

Introduction

According to DSM-5 (The Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders) the definition of Anorexia Nervosa must include the following criteria: restriction of energy intake leading to low body weight for age, sex, physical health and developmental trajectory, an intense fear of gaining weight (even though the person may be underweight), as well as body image disturbance. People who meet the AN criterion but are not underweight have atypical anorexia. It has been proved that there is no difference in the psychological and medical impacts between anorexia and atypical anorexia. [1]

Anorexia can affect people of all genders, ages, races, sexual orientations and ethnicities. The prevalence of AN is around 4% and usually, females are more affected with this disorder than males. [2]

Unfortunately, statistical epidemiology has shown that AN has the highest mortality rate of any psychiatric disorder, being associated with medical complications and comorbidities. [2]

Aim

As we have witnessed remarkable advances regarding the implication of genetics in many disorders, it has been proved that genetic factors are involved in the etiology of AN as well. The purpose of this review is to make a brief synthesis of the current knowledge regarding the genetic factors involved in AN disorder.

Material and method

The search platform used was PubMed and the searched terms were “anorexia nervosa”, “GWAS”, “genes” (August 2021). There were no filters added, except the fact that were taken into consideration only the articles published in the last 5 years.

Results

History of Genetics in Anorexia Nervosa

Among the first studies that demonstrated the implication of genetic factors in the development of Anorexia Nervosa were the family studies and the twin studies. By their contribution, it has been proved the familial aggregation of AN. In addition, the twin studies suggested that there might be a common genetic risk between AN and other psychiatric disorders such as eating disorders, major depression and obsessive-compulsive disorder. [3]

The candidate gene studies are based on the examination of the allele frequency of a selected SNP (single nucleotide polymorphism) in individuals that represent or not a trait of interest. In trying to reveal the risk genes for AN, the candidate gene studies did not add too many improvements to the genetic knowledge in AN. However it is important to mention that meta-analysis studies came to the conclusion that serotonin genes may be involved in the etiology of AN. They found a significant association between HTR2A polymorphism (specially, the A allele) and AN. There also was found an association between AN and short allele of 5-HTTLPR and a 5-HTT polymorphism. Unfortunately, these findings were not confirmed in further studies. [4]

There are many genes that contribute to the development of AN and as there are more and more advances of genomic experiments, genome-wide association studies have an important role in understanding the relationship between AN and genetics.

In 2010 a GWAS of both CNVs and SNPs in AN performed by Wang et al, confirmed that SNPs in OPRD1 gene and also SNPs near HTR1D confer risk for AN. Also, the study observed a recurrent 13q12 deletion (1.5 Mb) disrupting SCAS in two cases, and CNVs disrupting the CNTN6/CNTN4 region present only in AN cases. However, the study was not able to find genome-wide significant signals but emphasizes the importance of genomic studies in order to identify disease genes. [5]

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In 2014 Boraska and partners were able to identify variants in SOX2OT and PPP3CA genes that when significantly associated with AN, but these genes were previously known for association with Alzheimer's disease.[6] In 2015 a smaller GWAS confirmed that there is association between SOX2-OT gene and eating disorders, even though it could not reach genomic significance due to its limited size (only 184 cases). [7]

In 2017 a large and rigorous GWAS made on 4000 AN cases and 11000 controls was published. The study found a genome-wide significant locus on chromosome 12 (rs4622308), a region that was previously associated with some autoimmune diseases such as type I diabetes, asthma, rheumatoid arthritis. 6 genes from this specific region with genomic-wide significance were identified: ERBB3, RPL41, PA2G4, RPS26, IKZF4 and ZC3H10. The top SNP was found in ERBB3 gene. The study also made a LDSC (linkage disequilibrium score regression) which is a method used to discover genetic overlaps between disorders. Thus, there was observed significant correlation between AN and other disorders. More exactly, positive correlation was found between AN and schizophrenia, educational attainment, and high-density lipoprotein cholesterol and neuroticism and also, negative correlation between AN and glucose, insulin, and lipid phenotypes and body mass index. [8]

Also in 2017, it was published another GWAS that tried to reduce the phenotype heterogeneity by excluding the cases with AN that migrated to or from bulimia nervosa or binge eating disorder, making the assumption that this method will enhance gene discovery. The study managed to identify a genome-wide significant risk in EBF1 (Early B-Cell Factor 1) gene variants. This gene is known to encode a transcription factor necessary for the development of both osteoblast and adipocyte, mutations in this gene leading to low levels of circulating leptin. Therefore, this study suggested that a dysregulation in leptin signaling may have a role in the etiology of AN. [9]

In addition, an exome chip-based GWAS was conducted on more than 2000 cases of AN. The study also put emphasize on low frequency and rare variants. Although there were no findings that reached genomic-wide significance, there were identified two novel common variants rs10791286, an intronic variant in OPCM and rs7700147, an intergenic variant. [10]

Copy number variants also play an important role in developing psychiatric disorders. Therefore in 2017 was conducted the largest CNV genome-wide study in order to help to understand the role of CNVs in AN. It was investigated whether CNVs previously associated with psychiatric disorders were also present in AN. There was observed 2 cases of CNV in AN, one of them was previously associated with developmental delay, schizophrenia, and autism, and the other one was associated with AN in a previous pilot study. Moreover, there were also identified 40 new cases of large CNVs (more than 1Mbp size) from which five of them did not have any associated reports in CNV databases until then. [11]

Moving forward, in 2019 it was published the first GWAS that focused on de novo variants (DNVs) possibly involved in the risk genes of AN. DNVs represent mutations that are not found in the genome of the parents, but are found in the probands. Using the whole exome sequencing, it was analyzed a cohort formatted from nice females (aged 13-43) plus their families (mother and father). Focusing on de novo variants, it was discovered seven missense variants in potential genes: CSMD1, ZFHX2, PTPRD, CREB3, CYP4A11, TNFRSF6B, and GAB1. It is important to mention that four of these genes (CSMD1, CREB3, PTPRD and GAB1) are known for their presence in the same signaling pathways, specifically neuron differentiation pathway and dopamine pathway. Interestingly, PTPN11 (gene known to be involved in the etiology of Noonan syndrome) also belongs to this pathway and it was reported a case with a variant of PTPN11 in a patient with AN. PTPRD and CSMD1 were previously associated with addictions and psychiatric disorders. [12]

The largest GWAS ever made included 33 databases with almost 17000 cases of AN and 55 000 controls. Using meta-analysis for autosomes and chromosome X, the study was able to identify eight risk loci that reached genome-wide significance. Making the connection from loci to specific genes is not an easy task and, in order to achieve that, the study used three different perspectives: relationship to brain expression loci, regulatory chromatin interactions and the gene location within a GWAS locus. A number of 58 genes were identified by all three methods. Four of the single-gene loci identified were CADM1, MGMT, FOXP1 and PTBP2, concluding that these genes may contribute to the etiology of AN. Also, the study showed that AN shared genetic variations with some metabolic phenotypes (insulin resistance, type 2 diabetes, HDL cholesterol) and proved a bidirectional causal relationship between AN and BMI: AN risk alleles could increase the risk for low BMI and also the low BMI risk alleles could increase the risk for AN. In other words, the study suggested that metabolic dysregulation contribute to the difficulty of the patients with AN to maintain a healthy BMI. [13]

Lin Z. et al conducted a study that used the information provided from the previous GWAS meta-analysis mentioned above, suggesting that SNP (rs6589488) in CADM1gene might be in linkage disequilibrium with functional intronic variants or unknown variants. Therefore, in a cohort of 51 cases of AN, CADM1gene was screened by Sanger sequencing. There were found 13 SNPs from which 2 missense, 2 synonymous, 2 located at 5'-UTR and 7 intronic variants (including rs6589488). The conclusion was that the missense variants were not deleterious and that the initial intronic variant was not causative. However, the study encourages for further investigations as the causative variant might be in the vicinity of CADM1 gene, within 1Mb. It is interesting that one of the closest genes to CADM1 is NNMT (the nicotinamide N-methyltransferase) which is known to be associated with obesity. [14].

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Author	Publishing Year	Type of Study	Reached Genome Significance	Study Size	Main conclusions
Wang et al	2010	GWAS (SNPs)	no	1033cases AN; 3733 controls	HTR1D gene
Boraska et al	2014	GWAS (SNPs)	no	2907cases AN; 14860 controls	SOX2OT; PPP3CA
Duncan et al	2017	GWAS (SNPs)	yes	3495cases AN; 10982 controls	locus chromosome 12; ERB3;correlation with other diseases
Li et al	2017	GWAS (SNPs)	yes	692 females AN	EBF1;dysregulation leptin signaling
Huckins et al	2017	exome-chip based GWAS	no	2158 cases; 15485 controls	2 common variants
Yilmaz et al	2017	genome-wide CNV	no	1983 females	2 pathogenic CNVs; 40 new large CNVs
Bienvenu et al	2019	GWAS (DNVs)		9 females	7 missense variants in CSMD1,ZFHX2, PTPRD, CREB3,CYP4A11, TNFRSF6B, GAB1
Watson et al	2019	GWAS	yes	17000 cases; 55000 controls	8 risk loci; metabolic dysregulation
Lin et al	2020	GWAS	no	51 cases	variants in CADM1 gene

Table1. The main characteristics of the GWASs that were conducted regarding the genetic variants related to AN disorder.

Another study that is worth to be mentioned is about the association that was found between AN and OCD (Obsessive–Compulsive Disorder). Published in March 2021, the study used the information provided by the previous GWAS that were made on both AN and OCD and collected the tops SNPs for the risk genes of both disorders. Then, it was explored the phenotype, functional, spatiotemporal, and cell-specific patterns of these genes. What was found was that AN and OCD might have similar functional pathway, as the risk genes involved in both disorders led to alteration of the synapse transmission, by influencing the prefrontal cortex expressions. [15]

An important progress regarding genetics in AN is ANGI (Anorexia Nervosa Genetics Initiative), an international collaboration that collected information from 13 000 cases of AN. The countries involved in the trial are United States (US), Sweden (SE), Australia/New Zealand (ANZ) and Denmark (DK). The aim of this cooperative was to expand the samples for GWAS, and to provide efficient phenotyping regarding the phenotype. In addition, information provided could also be used for SNP-based genetic correlations and cross-disorder meta-analyses to identify variants shared with other psychiatric disorders. [16]

A step forward in the progress of genetics is made by EDGI: The Eating Disorders Genetics Initiative. EDGI represents an international organization whose aim is to explore the role of genes and environment in three major eating disorders: anorexia nervosa, binge eating disorder and bulimia nervosa. The countries that are taking part in the investigation are United States (US), Australia (AU), New Zealand (NZ), and Denmark (DK). The GWAS will include 14 500 cases of eating disorders and 1500 controls, becoming the largest genetic study ever conducted. [17]

Epigenetics is referring to all kind of biochemical mechanisms that result in changes in the activity of genes, but without changing the DNA sequence. The study of epigenetics is increasingly developing and methods in which epigenetics modifications can occur include DNA methylation, changing the chromatin conformation or non-coding RNAs. Although histone acetylation as an epigenetic method has not been studied too much, by this process the chromatin conformation is regulated, controlling the expression of many genes. Recently, a research published in 2019 discovered a potentially component in the etiology of AN- activity of the histone deacetylase 4 (HDAC4). HDAC4 is a member of the family of epigenetic modifier enzymes called histone deacetylases and is known to be implicated in the formation of the bone, central nervous system (CNS), muscle, and metabolism. The activity of HDAC4 might be altered either by genetic predisposition, fighter by environmental conditions such as: diet, increased levels of estrogen, physical activity. As these conditions could be potential "triggers" of AN, in this way HDAC4 may be involved in the cognitive factors of AN. Several studies

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demonstrated that there are significant methylation differences in HDAC4 locus in peripheral tissues of the patients with AN. [18]

Clinical Implications

The goal of all of this work and research regarding the implications of genetics in AN is that all the information will be used for the clinical care of the patients affected with the disorder.

The understanding of the role of genetics in AN can be used, first, for the psychoeducation of the patients and families. All the patients should be educated so that they will be aware of all the factors that can contribute to the etiology of their disease, including the genetic factors. A step forward was made by the Academy of Eating Disorders and other eating disorder organizations, when releasing the document "Nine Truths About Eating Disorders" in which Truth 7 and Truth 8 are stating "'Genes and environment play important roles in the development of eating disorders", respectively, "Genes alone do not predict who will develop eating disorders".[19]

Another aspect to be taken into consideration is that by identifying the genetic markers of risk, we would be also able to identify those who are at high risk. Once we identify we can put all our efforts towards prevention because is always better to stop the disease before it starts.

Furthermore, all the genetic correlations that were found between AN and other diseases can be used for further investigations and for a better understanding of the genes that can be specific pharmaceutical targets for the disorder. As AN is a difficult-to-treat illness, all the information provided by GWAS can help in finding pharmaceutical agents that will innovate the treatment for AN. [2]

Conclusions

To conclude, there has been made substantial progress in understanding the genetic architecture of AN and its relation to other disorders, but there is still room for more. AN represents a difficult treat-to treat illness and there is a desperate need to discover an efficient therapeutic method for patients with this disorder. Therefore, all the research that has been made until now should lead to motivation and encouragement for further investigations and follow-up studies. The main goal is that all the genetic information to be used directly in the treatment and prevention of AN.

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