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THE STARTING POINT OF EATING DISORDERS: ROLE OF GENETICS

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SUMMARY

Eating disorders are perplexing diseases of which the etiology is still unknown. Recent research has focused on the possibility that genetics plays a role in vulnerability to these pathologies. This study gives an overview of the available literature focusing on family, twin and molecular genetic studies of eating disorders.

Key words: *eating disorders - genetic factors - candidate genes*

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INTRODUCTION

Although they have been known since ancient times, Eating Disorders (EDs) have only recently found their nosographic autonomy. EDs rank among the 10 leading causes of disability among young women and anorexia nervosa (AN) has the highest mortality rate among all mental disorders. The phenomenon of EDs affects about 10% of young women in the western world although their etiology is still unknown. An interaction between genetic and environmental factors seems to explain the pathogenesis. However other epidemiological data are necessary for the identification of risk factors; the biopsychosocial construct seems a viable base of operations. The influence of genetic factors has been evaluated by different research groups and twin studies have estimated a heritability of about 50%. As regards environmental factors, the risk of EDs seems to be affected by socio-cultural factors, stressful events and sexual abuse, perinatal factors, psychological characteristics and behaviors such as perfectionism, negative affectivity, dieting, social and mass-medial pressing (Striegel 2007, Favaro 2003).

Anorexia Nervosa (AN) diagnosis was introduced by Gull and Lasègue in the 1873 and after one century, in 1979, Russel introduced the diagnosis of Bulimia Nervosa (BN) (Vandereycken 1989). More recently has been described a new psychopathology called Binge Eating Disorder (BED). Finally, a variety of psychopathologies have been identified as Eating Disorders Not Otherwise specified (EDNOS) (APA 2000). Each of them is described by different phenotypic traits that are indicated below:

Anorexia Nervosa

Anorexia Nervosa (AN) is characterized by self-induced starvation and excessive weight loss; it is a mental disease with severe metabolic effects on the whole body. AN is the 3rd most common chronic illness among adolescents and it has the highest mortality rate among all psycological disorders. Two different subtypes of AN are known such as Restricting Anorexia Nervosa (ANR) and Binge Purging Anorexia Nervosa (ANBP).

Bulimia Nervosa

Bulimia Nervosa (BN) is characterized as bingeing (execessive or compulsive consumption of food) and purging (getting rid of food and also inappropriate use of laxatives, diuretics, enemas etc). Up to 19% of college-aged girls struggle with Bulimia.

Binge Eating Disorder

Binge Eating Disorder (BED) is characterized as recurring episodes of eating significantly more food in a short period of time with episodes marked by feelings of lack of control. BED is the most common eating disorder in the U.S. Obesity is the most common complication.

Feeding Eating Disorders Not Elsewhere Classified

Feeding Eating Disorders Not Elsewhere Classified (FED-NEC) is characterized as disturbances in eating behavior that do not necessarily fall within a specific category of AN, BN or BED. It is the most common eating disorder diagnosis. However other eating disorders have been identified such as: *Ortorexia* that is defined as an obsession with "healthy or righteous eating", *Bigoressia or Muscle Dysmorphia* that is a constant obsession to have underdeveloped muscle mass and/or underweight with a distorted self-images.

Night Eating Disorder

Night Eating Disorder (NES) that is characterized by a persistent habit of binge eating night (DSM V 2014) (Alliance for eating disorders).

A number of reports suggest the involvement of genetic factors in EDs. In this review, we evaluate the current status of genetic studies that identified the candidate genes that may influence the vulnerability to these important diseases.

MOLECULAR GENETIC STUDIES

In the past 30 years, human genetic studies have identified more than 1000 genes responsible for human diseases. The aim of molecular genetic studies is to identify chromosomic regions and candidate genes involved in the etiopathogenesis of human diseases such as eating disorders, using two different approaches: linkage studies and association studies (Juli 2012).

Linkage studies

A linkage study of a heterogeneous sample of individuals with a broad range of defined EDs produced findings which were not statistically significant; however, when the sample was restricted to relative pairs exhibiting the classic Restricting Anorexia Nervosa (ANR), a significant linkage has been found on 1p33-1p36 region on chromosome 1 (Bergen 2003). An additional study has confirmed this data and it was observed that in the 1p33-1p36 region there are two genes that intersected with pathophysiological theories of the etiology of Anorexia Nervosa and that have been considered in the association studies of EDs: the delta opioid receptor (OPRD1) and the serotonin 1D receptor (HTR1D) (Bulik 2007).

When the linkage analysis were performed considering not only the illness but other phenotypic characteristics related to it, a significant number of signals were observed such as obsessionality at 6q21, anxiety at 9p21.3, body mass index at 4q13.1, concern over mistakes at 11p11.2 and food-related obsessions at 17q25.1 and 15q26.2 (Bulik 2003).

There is only one study that found a significant linkage between Bulimia Nervosa (BN) and 10p13-p12 chromosomal region and another linkage with low significance in the 14q region (Blundell 1987).

No linkage studies exist for Binge Eating Disorder (BED).

Association studies

A number of association studies have been performed to identify candidate genes for EDs. Central and peripheral neurotransmitters, hormones and peptides have been shown to regulate eating behavior and also psychopathological dimensions associated to EDs. Indeed, the genes involved in the biosynthesis and/or degradation of those substances and their receptors have been considered as candidate genes, and polymorphisms of those genes appear of particular interest, especially if they affect either the protein structure/function or expression (Monteleone 2008).

Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) is involved in a vast range of biological, physiological and behavioral functions (Halford 2000). Several studies implicate 5-HT in body weight regulation and more specifically in eating behavior (Scherag 2010) and eating disorders (Brewerton 1996). However, 5-HT has been shown to be involved also in psychopathological traits associated with EDs, such as depression, anxiety, impulsivity and obsessionality (Lucki 1998). The serotonergic system includes tryptophan hydroxylase, the 5-HT transporter (5-HTT) and different subtypes of 5-HT receptors; all of them have been considered during association studies of EDs. A polymorphism in the promoter region of the 5-HTT gene has been identified (Heils 1999) and it is represented by a 44-base pair deletion (short or S variant) or insertion (long or L variant). In the case of AN, seven studies investigated the association with this polymorphism and two of them found a nominal association of the S allele with AN (Fumeron 2001, Matsushita 2004), while the remaining ones did not confirm it (Hinney 1997, Di Bella 2000). The polymorphism in the promoter region of the 5-HTT gene has been analyzed also in BN by four studies (Matsushita 2004, Di Bella 2000, Gorwood 2004), and only one of them showed a positive association between the S allele and BN in a small group of patients (Di Bella 2000). A higher frequency of the L allele was detected in BN female patients (Monteleone 2008) that would imply lower 5-HT concentrations at central synapses, which could be responsible for reduced satiety and binge eating behavior. In the case of BED, only one study found a higher frequency of both LL genotype and L allele in a small group of obese women with BED respect to normal weight healthy females (Monteleone 2006). The polymorphism 1438 G/A of the 5-HT2A receptor gene has been studied for both AN and BN. In the case of AN, six studies had positive results of association (Collier 1997, Sorbi 1998, Ricca 2002) but eight studies and a meta-analysis did not confirm it (Rybakowski 2006, Hinney 1997, Campbell 1998, Ziegler 1999). For BN, the association of 1438 G/A polymorphism in the promoter region of the 5-HT2A receptor gene was evaluated in eight studies: five of them were negative (Enoch 1998, Nacmias 1999, Ziegler 1999) and three were positive (Ricca 2002, Ricca 2004, Nishiguchi 2001). No study has tested the association between polymorphisms of the 5-HT2A receptor gene and BED. However, other subtypes of 5-HT receptor were evaluated such as 5-HT2C with positive results for AN and negative results for BN and BED (Monteleone 2008); the association between a polymorphism in the 5-HT1Dβ receptor was studied as well for both AN and BN with positive results (Monteleone 2008).

Dopamine

Dopamine (DA) has been implicated in the pathophysiology of AN and BN (Kaye 1999, Golden 1994). In fact, main symptoms related to AN like revulsion to food, weight loss, hyperactivity, distortion of body image, and obsessive-compulsive behavior have all been related to dopamine activity (Kaye 2004). Association studies between polymorphisms in the dopamine D4 receptor gene (DRD4) and AN have been studied giving positive (Bachner-Melman 2007) and negative results (Hinney 1999, Karwautz 2001). The

polymorphism 7-repeat allele of the DRD4 exon 3 repeat, seems to be relevant for BED and BN: in particular, an elevated rate of binge eaters in a group of carriers of the 7-repeat allele was identified (Levitan 2004). Seven polymorphisms within the dopamine D2 receptor gene (DRD2) were identified, and two of them were found to associate with AN (Bergen 2005). However, Nisoli et al., has confirmed the association with AN or BN.

Catechol-o-methyl transferase

Catechol-o-methyl transferase (COMT) is an enzyme that catabolizes brain catecholamine neurotransmitters such as dopamine and norepinephrine. The gene contains a much studied polymorphism Val158Met that was suggested to influence the susceptibility to AN (Frisch 2001). However, some studies did not confirm this data (Gabrovsek 2004, Bergen 2005), so these findings require replication in large independent samples or at least in a meta-analytical approach (Scherag 2010).

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is expressed in the hypothalamic nuclei associated with weight regulation and feeding control. Humans with low serum BDNF levels show an aberrant eating behavior (Monteleone 2005, Saito 2009). A number of studies analyzed the role of the BDNF non-synonymous polymorphism Val66Met in the etiology of EDs. This polymorphism was found to be associated with AN restricting type in a Spanish sample (Ribasés 2003) and with binge eating/purging AN in a case-control study of 1,142 Caucasian patients with EDs consecutively recruited in six different centers from five European countries (France, Germany, Italy, Spain and UK) (Ribasés 2004). Monteleone et al. evaluated the association of the Val66Met polymorphism with both BN and BED, and results were negative; however an association between the AA genotype and the severity of binge-eating (considered by the weekly frequency of bingeing and the BITE symptom and total scores) was detected in both patients groups (Monteleone 2006). On the other hand, polymorphisms of the NTRK2 gene, which encodes a BDNF receptor, have been investigated for association with AN and BN in a single study with some positive results (Ribases 2005).

Endocannabinoid system

Endocannabinoid system is recently considered of scientific interest for EDs. Both endogenous and exogenous cannabinoids stimulate food intake through activation of the cannabinoid receptor 1 (CNR1). The orexigenic effects of cannabinoids are mediated not only by CNR1 but also by endocannabinoid degrading enzymes fatty acid amide hydrolase (FAAH), N-acylethanolamine-hydrolyzing acid amidase (NAAA) and monoglyceride lipase (MGLL). Siegfried et al. investigated an (AAT)n repeat in the downstream flanking region of CNR1 and found that the 14-repeat allele was preferentially transmitted in the binge eating/purging AN group, while the 13-repeat allele was more often transmitted in the restricting AN group. Another study on the endocannabinoid system in AN patients concerned to the previously described (AAT)n repeat as well as a total of 15 polymorphisms in CNR1, FAAH, NAAA or MGLL in up to 91 German AN trios, exists. Evidence for association (measured by transmission disequilibrium test) of any of the polymorphisms or the (AAT)n repeat in AN was not detected (Müller 2008). It is interesting that enhanced concentrations of circulating endocannabinoids have been reported in overweight/obese patients with BED (Monteleone 2005).

Estrogen receptors

Estrogen receptors (ESR) have been considered other candidate genes because of the female predominance in EDs. This suggests a role for sex hormones, especially estrogens, in the etiopathogenesis of EDs (Monteleone 2008). The polymorphism 1082G/A of the ESR2 gene has been found associated with AN in two independent case-control studies (Rosenkranz 1998, Eastwood 2002). The polymorphism 1730A/G of the ESR2 gene has been found associated with BN in one study (Nilsson 2004) but it was not confirmed in another one (Rosenkranz 1998). On the other hand, no association of polymorphisms of the ESR1 gene with AN was detected in a single case-control study (Eastwood 2002). However other candidate genes were analyzed in association studies such as norepinephrine transporter gene (Urwin 2003), leptin (Hinney 1999), the agouti-related protein (AGRP) (Vink 2001), tumor necrosis factor α (TNF-α) (Ando et al. 2001, Slopien et al. 2004), phospholipase A2 (Slopien 2004) and uncoupling protein 2,3 (UCP-2/UCP-3) (Campbell 1999, Hu 2002).

FAMILY AND TWIN STUDIES

It has been reported that there is a high frequency of AN and BN in relatives of probands with an ED compared to relatives of healthy controls, which suggests a familial aggregation for AN and BN (Gorwood 2003, Kipman 1999). The first-degree relatives of AN patients have an average 2.69% lifetime risk of AN, compared to 0.18% in relatives of healthy controls (Gorwood 2003). Other studies revealed coaggregation of AN and BN, with relative risks of AN of 11.3 and 12.3, respectively, and relative risks of BN of 4.2 and 4.4, respectively, in first degree female relatives of probands with AN or BN (Lilenfeld 1998, Strober 2000). Hudson et al. evaluated 300 probands with and without BED, and 888 first-degree relatives. It has been demonstrated that really BED runs in families and the estimated heritability in BED patients was around 57% (Hudson 2006). These studies demonstrate that specific genes can determine familial vulnerabilities and predispose individuals to EDs. To evaluate the genetic contribution in the development of EDs, it needs to consider twin studies, since differences between a pair of monozygotic twins (MZ)

result only from environmental factors, whereas differences between dizygotic twins (DZ) could be due to either genetic or environmental factors. It has been shown that there is a higher concordance rate of AN or BN in MZ twins than in DZ twins, which implies that genetic factors may explain why EDs are common in families. For AN aheritability from 48 to 88% has been estimated and for BN from 28 to 83% (Bulik 2000, Kipman 1999, Bulik 1998). For BED the heritability is almost 50% (Bulik 2000). A large twin study by screening all living twins in the Swedish Twin Register (n=31,406) has estimated an heritability of 56% for AN (Bulik 2006) and from 50 to 83% for BN. A number of twin studies have focussed more specifically on several ED-related traits such as binge-eating, self-induced vomiting, drive for thinness and dietary restraint demonstrating that there is a high heritability among them (de Castro 2005, Bulik 2006). The influence of genetic and environmental factors on ED-related behaviors has been studied in prepubertal and post-pubertal 11 year old twin girls compared to a 17 year old post-pubertal twin. In both post-pubertal 11 year old and 17 year old girls, genetic effects were significant whereas shared environment was not (Klump 2006). These data suggest that puberty may be a critical period when some genes that make individuals more susceptible to the development of eating disorders (Scherag 2010) are activated. A shared genetic transmission between EDs and anxiety disorders in adolescent MZ female twins is also reported, suggesting that genetic vulnerability to EDs might be associated with genes involved in anxiety (Keel 2005).

CONCLUSIONS

The etiology of EDs is currently unknown; however molecular genetic studies and family/twin studies suggest that a strong genetic contribution is likely to be involved. However, only a few linkage studies have been performed and the results have been often inconsistent. These data surely are in an early phase and other research works are necessary to clarify the role of genetics in these pathologies. A combination of linkage, association and other approaches will probably be necessary. Reasons for such prevalently negative results are multiple, but the heterogeneity of clinical phenotypes is likely to be the most relevant one. The identification of endophenotypes (i.e. traits associated with the disease that are heritable) in EDs will help to identify more homogenous subgroups of patients in order to reduce the potential obscuring effects of focusing on currently categorized complex syndromes (Monteleone 2008).

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